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ENDOCARDIAL TUBERCULOSIS

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Two cases of involvement of the endocardium by tuberculosis were encountered at necropsy (cases 1 and 6 in the present study). These cases were interesting in themselves, but they gave rise to such questions as the following:

How often does tuberculosis involve the endocardium? What part of the endocardium is usually affected? Does the lesion occur by direct implantation on the inside of the heart or through the coronary arteries? Are there cases of tuberculous endocarditis of the valves analogous to those of rheumatic and bacterial valvular endocarditis? Are any of the chronic or healed endocarditides caused by tuberculosis? Is there such a thing as toxic endocarditis when there is widespread tuberculosis elsewhere in the body?

The study reported here was made in an attempt to answer these questions.

The source material consisted of the autopsy and preserved specimens of the Duke Hospital, the autopsy records at Johns Hopkins Hospital, personal observations on material in museums of two other medical schools and the voluminous literature on tuberculous endocarditis and tuberculosis of the heart in general.

There are several reviews [1] which touch on endocardial tuberculosis

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1. The more complete studies are: (*a*) Heineman, H. N.: Lancet **2**: 1792, 1901. (*b*) Marshall, H. T.: Bull. Johns Hopkins Hosp. **16**:303, 1905. (*c*) Huebschmann, P.: Pathologische Anatomie der Tuberkulose, Berlin, Julius Springer, 1928, p. 147. (*d*) Pic, A., and Morenas, L.: La tuberculose cardio-vasculaire, Paris, Gaston Doin & Cie, 1930. The less complete reports are: (*e*) Cornil, V.: L'abeille méd. **41**:473, 1884. (*f*) Kundrat: Wien. med. Bl. **8**:239, 1885. (*g*) Kidd, P.: St. Barth. Hosp. Rep. **23**:252, 1887. (*h*) Orth, J.: Lehrbuch der speciellen pathologischen Anatomie, Berlin, A. Hirschwald, 1887, vol. 1, p. 196. (*i*) Osler, W.: Johns Hopkins Hosp. Rep. **2**:62, 1891. (*j*) Biondi, D.: Centralbl. f. allg. Path. u. path. Anat. **6**:105, 1895. (*k*) Benda, C.: Ergebn. d. allg. Path. u. path. Anat. **5**:455, 1898 (*l*) Harbitz, F.: Deutsche med. Wchnschr. **25**:124, 1899. (*m*) Anders, J. M.: J. A. M. A. **39**:1081, 1902; Am. J. M. Sc. **123**:93, 1902. (*n*) Thorel, C.: Ergebn. d. allg. Path. u. path. Anat. **9**:886, 1903. (*o*) Norris, G. W.: Am. J. M. Sc. **128**:649, 1904. (*p*) Braillon, L., and Hautefeuille, P.: Compt. rend. Soc. de biol. **59**:394, 1905. (*q*) Brown, Lawrason: Am. J. M. Sc. **137**:186, 1909. (*r*) Ribbert, H., in Henke, F. and Lubarsch, O.: Handbuch

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and tuberculous endocarditis. However, none goes deeply into the subject or analyzes the reported cases critically.

Tuberculosis of the endocardium was found six times in about nine hundred consecutive necropsies at Duke Hospital. It occurred in five cases (cases 1 to 5 of the present series) of generalized miliary or disseminated tuberculosis as a part of the generalized process. There were scattered tubercles varying from microscopic size to that of a pea. They occurred on all parts of the endocardium, including the valves.

In one case (case 6) the endocardial process resulted from the extension of pericardial and myocardial tuberculosis through the cardiac wall. The organs were available from a similar case in which the autopsy was performed at the Baltimore City Hospitals.

REPORT OF CASES

A case of generalized miliary tuberculosis with a miliary tubercle on the tricuspid valve is presented first.

CASE 1.—A Negro, aged 29, had night sweats ten months before death; a cough developed six months later, and he died of tuberculous meningitis. Clinical examination of the heart revealed no abnormality.

Macroscopic Examination.—Generalized miliary tuberculosis and tuberculous meningitis were noted. The oldest tuberculous lesion seen consisted of large caseous and scarred mediastinal lymph nodes. Miliary tubercles were thickly and uniformly scattered throughout the lungs and spleen and occasionally were seen in the kidneys.

The heart weighed 300 Gm. At the base of the tricuspid valve lay a single round, grayish-red nodule, 2 mm. in diameter. Otherwise the heart appeared normal.

Microscopic Examination.—The tubercles in any one of the organs were fairly uniform in size. A single tubercle in the lungs measured just less than 1 mm. in diameter; those in the liver, spleen, pancreas and vertebrae were smaller, and those in the kidneys and suprarenals were larger, measuring from 2 to 3 mm. in diameter. Two tubercles projected into the lumen of a small vein in the kidney. They were separated from the blood by intact endothelium at the level of the section. Numerous acid-fast bacilli were stained in the meningeal exudate.

The tubercle at the base of the tricuspid valve (fig. 1) measured 2 by 1.5 mm. Slightly more of the tubercle lay on the valve than on the atrial wall above. Scattered striated fibers of cardiac muscle extended downward to its upper pole. Around a caseous center was a peripheral shell of granulation tissue. The endothelium of the valve could not be traced to the free surface of the tubercle. No thrombus or fibrin overlay the tubercle. An elastic tissue stain demonstrated that the greater part of the tubercle, approximately the basal two thirds, lay external to the strand of elastic tissue continuous with that of the atrial endocardium above

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der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 205. (*s*) Vaquez, H., and Laidlaw, G.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1925, p. 263. (*t*) Aschoff, L.: Pathologische Anatomie, ed. 7, Jena, Gustav Fischer, 1928, vol. 2, p. 30. (*u*) Halbron, P.: Paris méd. **1**:407, 1933. (*v*) Mouquin, M.: Nouveau traité de médecine, Paris, Masson & Cie., 1933, vol. 10, p. 145. (*w*) Prieur, R.: ibid. pt. 2, p. 749.

and of the valve below. (By external is meant on the side toward the valve and the myocardium.) In figure 1, in which the elastic tissue is not stained, the strand of elastic tissue passes just internal to the caseous center.

A half-dozen tubercle bacilli were stained in the peripheral ring of granulation tissue, some of them lying close to its free surface. Loeffler's counterstain of methylene blue showed the absence of other organisms in the tubercle and on the free surface.

Sections at other levels, in which the area of the tubercle was less extensive, showed a greater proportion of the tubercle on the internal side of the strand of elastic tissue.

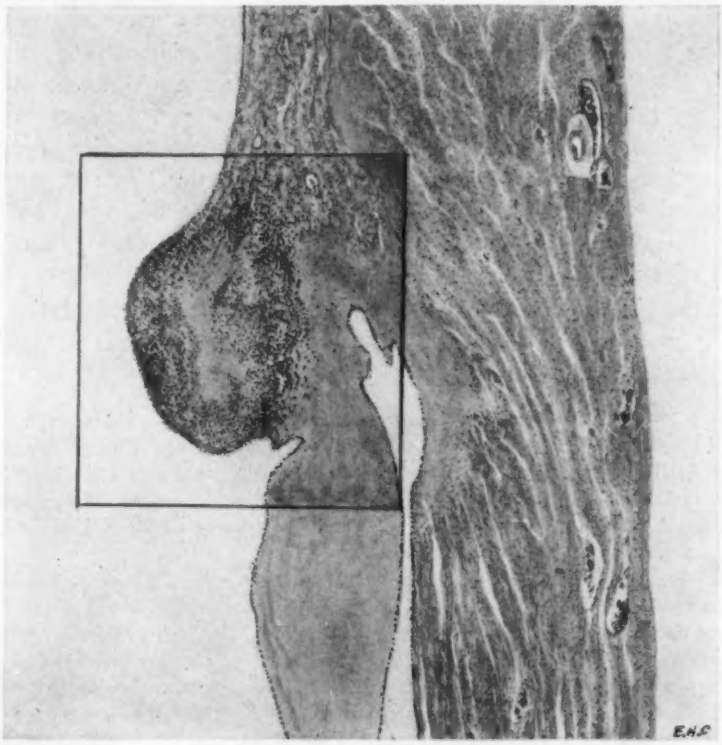

Fig. 1 (case 1).—Endocardial tubercle at the base of the tricuspid valve. The tubercle was part of generalized miliary tuberculosis (× 16).

The tubercle was similar in size and structure to those in the kidneys and suprarenals. Other sections of the heart showed a much smaller endocardial tubercle with intact endothelium, extending into the cardiac muscle and containing tubercle bacilli and two minute intramuscular tubercles. All the latter lesions were sectioned by chance. No other tubercles occurred in several large sections of cardiac muscle.

In brief, at the base of the tricuspid valve in the heart of a patient dying of generalized miliary tuberculosis lay a small tubercle. It seemed to be part of the generalized process, though it was larger than most

of the miliary tubercles in the body, because of the similarity in size and structure to the miliary tubercles in some of the other organs. Tubercle bacilli may have been dispersed from the tubercle, since bacilli were noted close to the free surface and the overlying endothelium was absent. It is not entirely clear that the absence of endothelium was not an artefact, especially since no thrombus or fibrin occurred there. Because of the small size of the tubercle, its similarity to tubercles elsewhere and the presence of other intravascular tubercles, as demonstrated in a renal vein, there is no reason to believe that the endocardial tubercle was the main point of rupture in the genesis of the miliary tuberculosis.

The tubercle was too large for one to determine whether it had arisen directly from the inside of the heart or by way of branches of the coronary arteries, which may or may not be present normally at the base of this valve. In any event, it did not appear to arise from the myocardium, since it lay chiefly on the dense fibrous tissue at the base of the valve. The fact that the tubercle lay largely beneath the elastic layer is not believed to prove that it did not arise from the endocardium. This point will be considered later.

A case in which a caseous endocardial tubercle showed particularly well is now presented. It was thought to be part of the generalized disseminated tuberculosis.

CASE 2.—*Macroscopic Examination.*—The body was that of a woman of 19, who had given birth to an apparently normal infant three and one-half weeks before death. Tuberculosis of the tracheobronchial lymph nodes and disseminated tubercles in the lungs, bronchi, pleura, peritoneum, liver, spleen, kidneys and heart were noted. The tubercles in the lung and spleen measured from 2 to 3 mm. in diameter. Those in the liver were slightly smaller.

The heart weighed 210 Gm. The epicardium over the right ventricle bore a flattened tubercle, which measured 4 mm. in diameter and extended slightly into the cardiac muscle. A similar epicardial nodule 3 mm. in diameter extended more deeply into the left ventricle. Otherwise the epicardium appeared normal. No myocardial tubercles were observed, even after gross serial sections of the entire heart were made at intervals of less than 1 cm. All the valves were delicate. The general endocardial surface appeared normal, with the exception of the tubercles to be described.

On a trabecula near the apex of the right ventricle lay a smooth, droplike, yellowish nodule measuring 2 mm. in diameter and projecting well above the surface of the trabecula. On section it seemed to lie on the endocardium and apparently did not extend into the muscle. On a trabecula and 1.5 cm. below the posterior cusp of the aortic valve lay another tubercle (fig. 2). A similar tubercle was embedded between the trabeculae of the anterior wall of the left ventricle. None of these tubercles was ulcerated.

Microscopic Examination.—About a score of sections were cut at regular intervals through the tubercle shown in figure 2. They showed a caseous center in the tubercle. No endothelial lining could be followed over the free surface, and no thrombus overlay the tubercle. The major part of the tubercle lay superficial to the elastic strands. However, the tubercle was already too large

to furnish any indication that it had started in the endocardium and extended to the myocardium or vice versa.

Large numbers of tubercle bacilli were stained in the caseous center and also among the more superficial cardiac muscle fibers. The methylene blue counterstain showed no other organisms.

On the aortic cusp of the mitral valve, just at the line of closure, a translucent nodule less than 1 mm. in diameter was seen. This nodule was cut into serial sections for microscopic study and proved to be a small fibrous nodule, the nature of which was not clear. However, at one side of it and embedded in the leaflet was a collection of lymphocytes and plasma cells without necrosis or special resemblance to a tubercle. The endothelium on both sides of the leaflet at this point was intact. Bacterial stains failed to show either tubercle bacilli or other

Fig. 2 (case 2).—Endocardial tubercle on a trabecula of the left ventricle. The tubercle was part of generalized miliary tuberculosis.

organisms. This lesion is described only because it is similar to lesions mentioned by de Vecchi [2] as forms of "toxic" endocarditis. Whether in this case the lesion was a part of the tuberculous process is, of course, not clear.

A blood culture showed no growth. (The culture was not made for the purpose of obtaining a growth of tubercle bacilli.) Material from a tubercle from the liver was planted on special mediums in an attempt to produce a growth of a fungus, but, as was to be expected, none was obtained.

Endocardial tubercles were especially numerous in the following case, some of which were superficial.

2. de Vecchi, B.: Arch. Path. **12**:48, 1931.

CASE 3.—*Macroscopic Examination.*—In a Negro girl, aged 6 years, generalized miliary tuberculosis and tuberculous meningitis were noted. Tubercles were more conspicuous in the kidneys and spleen than elsewhere, except in the lungs. Here they measured less than 0.5 mm. in diameter and were placed from 1 to 2 mm. apart.

The heart showed an extraordinary number of minute tubercles on the inner surface. On gross examination it was, of course, impossible to distinguish the endocardial from the more superficial myocardial tubercles, because of the transparency of the endocardium. The inner lining of the right ventricle, below the pulmonic valve, bore a tubercle 0.5 mm. in diameter. Two smaller tubercles were close by. Another occurred on the interventricular septum beneath the attachment of a chorda tendinea of the tricuspid valve. Eight minute tubercles were visible in the left atrium and six in the left ventricle. Several occurred on papillary muscles. On the upper surface of the aortic cusp of the mitral valve, one exceedingly minute fleck was visible half-way between the base of the leaflet and its free border. Another tubercle lay approximately at the line of closure. None occurred on the pulmonic valve.

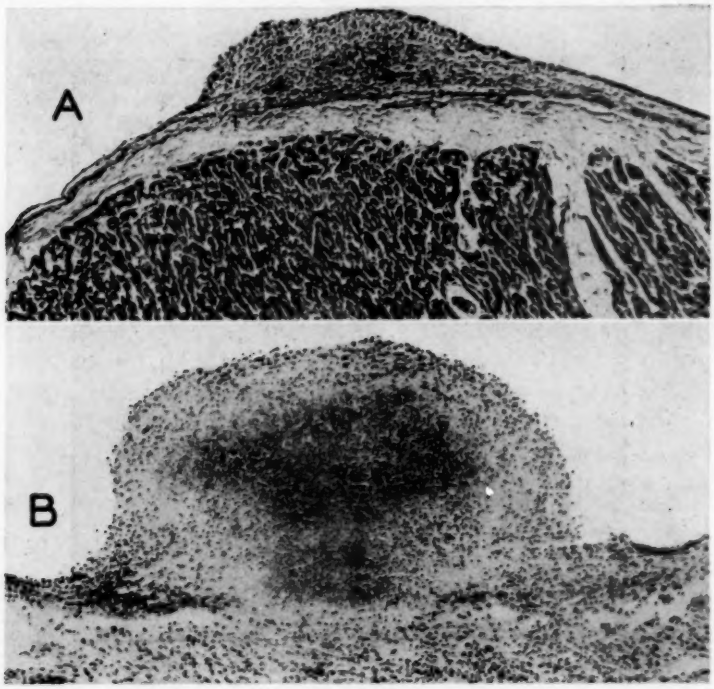

Fig. 3.—*A* (case 3) represents a superficial endocardial tubercle on a papillary muscle. Weigert's elastic tissue stain; ×60. *B* (case 4) shows a superficial endocardial tubercle, sectioned serially at the level in which the tubercle extended most deeply (×60).

Microscopic Examination.—A tubercle at the apex of the largest papillary muscle of the left ventricle was cut at four levels. Microscopically, at each level it appeared superficial. An elastic tissue stain (fig. 3*A*) showed that no part

of the tubercle reached the myocardium or even the deeper part of the endocardium. The flat, noncaseous lesion consisted of large mononuclear cells. Between them was a fibrillar network, representing in part the fibrillar tissue of the endocardium and in part newly formed reticulum. No fibroblasts, few lymphocytes and no polymorphonuclear cells could be identified. There was nowhere the appearance of a thrombus. The endothelium could be followed to the lesion but not over the center. Throughout the lesion there were acid-fast bacilli, both intracellular and free. In addition, cocci in chains and large bacilli which stained with methylene blue were seen in the superficial part of the lesion. None lay as deeply within the lesion as some of the acid-fast organisms. Organisms stained with methylene blue were seen also on and in the endocardium beyond the confines of the lesion, but no acid-fast organisms were noted. It was thought that the organisms staining with methylene blue had grown post mortem, especially since there was no polymorphonuclear reaction about them. The lesion was regarded as primarily and essentially tuberculous. No fibrin could be identified on morphologic grounds in the hematoxylin and eosin sections. Weigert's differential stain for fibrin failed to bring out fibrin; it did, however, show the gram-positive cocci and bacilli.

In the same block was another tubercle, interpreted as being primarily subendocardial or myocardial. Here there was caseation, the greater part of which lay in the myocardium. However, the endocardial involvement was apparent. At another level, the tubercle appeared to lie wholly within the endocardium, indicating that the lesion became more superficial in its peripheral part. Tubercle bacilli occurred in this tubercle. Pyogenic organisms were also present in the superficial part as in the tubercle just described.

Complete serial sections of the flecks on the mitral valve showed superficial collections of large mononuclear cells and fibrillar strands, resembling on a small scale the tubercle shown in fig. 3*A*. No tubercle bacilli could be stained in several sections. Organisms of various types staining with methylene blue were seen in the flecks and also in the adjacent normal valvular tissue. No etiologic significance was attached to them. The flecks were regarded as tubercles.

Sections cut at intervals through the central portion of each pulmonic cusp failed to show lesions. The investigators who have studied the vascularity of valves have described no vessels in this region—even those who upheld the idea that normally the valves are vascular. Hence, it was thought that the presence of lesions in this avascular region would be strong proof that tuberculous endocardial lesions can develop directly from the blood in the cavity of the heart. The failure to find tubercles here does not indicate that tubercles cannot develop directly from the blood of the cavity.

Sections from another block showed a mononuclear reaction with necrosis on the surface of the tip of a papillary muscle and on the attaching chorda tendinea. This was thought to be a tuberculous lesion. No thrombus formation was associated with it.

Two large sections of the myocardium showed only two intramuscular tubercles.

In the spleen no tubercle bacilli and no organisms staining with methylene blue could be observed. Acid-fast organisms were demonstrated in the lungs and meninges.

In another case of generalized miliary tuberculosis, superficial endocardial tubercles were observed.

CASE 4.—*Macroscopic Examination.*—The lungs of a Negro boy, aged 20 months old at death, were uniformly studded with caseous tubercles, measuring from 2 to 3 mm. in diameter and lying from 2 to 5 mm. apart. Tubercles in the liver, spleen, kidneys and brain were about the same size but lay much farther apart. Tuberculous meningitis was present.

The heart weighed 65 Gm. The right side was dilated. No tubercles were seen on the smooth and shiny visceral pericardium. On a trabecula of the right side of the interventricular septum, half-way between the tricuspid valve and the cardiac apex, lay an irregularly shaped, broad-based, smooth-surfaced, grayish-yellow, caseous tubercle, measuring 1.5 mm. in diameter. Below it was a similar one less than 1 mm. in diameter. Section showed that they scarcely extended into the musculature. Farther toward the apex lay another slightly larger caseous nodule, mostly embedded in muscle. No tubercles were seen elsewhere on the parietal or valvular endocardium. Consecutive gross sections 3 mm. apart throughout the myocardium showed only one myocardial tubercle visible to the naked eye. This tubercle lay deeply embedded in the left ventricle.

Microscopic Examination.—Serial sections of the superficial endocardial tubercles were made. The larger tubercle lay on and in the endocardium and extended into the myocardium slightly. The smaller nodule, in the sections near the periphery, did not involve the myocardium. The section in which the tubercle extended most deeply is shown in figure 3*B*. The center was caseous. There was no fibrin or thrombus on the free surface. The extension of the tubercle into the musculature was only in the form of scattered lymphocytes. Elastic tissue stains showed that the main strands of elastic tissue of the endocardium passed along the base of the tubercle just above the myocardium and were not displaced into the superficial layers of the tubercle. This fact, together with the superficial location of the tubercle, suggested that the tubercle arose from the endocardium rather than from the underlying muscle.

Even after prolonged search no organisms of any kind could be seen in sections of the endocardial tubercles stained with carbolfuchsin and Loeffler's methylene blue. However, tubercle bacilli were noted in the pulmonary tubercles.

Microscopic examination of the scattered tubercles in other organs showed them to be similar to the endocardial tubercles.

It was thought that in this case there was much circumstantial evidence that the endocardial tubercle which is illustrated in figure 3*B* arose from the free surface of the endocardium or from the endocardium itself rather than from the myocardium.

Another case of generalized miliary tuberculosis is presented, occurring in a middle-aged person in whose heart endocardial tubercles of varying sizes were seen.

CASE 5.—*Macroscopic Examination.*—At necropsy tubercles measuring from 1 to 2 mm. in diameter were noted in the lungs and spleen. In addition, there were myriads of much finer tubercles in the lungs, liver, spleen and elsewhere. Tuberculous meningitis was also present.

The heart weighed 260 Gm. At the base of a leaflet of the pulmonic valve on the ventricular aspect lay a projecting, caseous nodule, measuring 1 mm. in diameter. It corresponded to the larger tubercles of the lungs and spleen. At the base of a papillary muscle on the same side of the heart was a minute white dot.

A similar nodule occurred on a trabecula toward the apex of the right ventricle. The smaller tubercles corresponded to the smaller ones in the lungs and other viscera. Gross serial sections at intervals of about 0.5 cm. throughout the whole heart showed only 1 macroscopically visible tubercle in the myocardium.

Microscopic Examination.—A section through the nodule beneath the pulmonic valve showed a caseous tubercle lying mostly in the endocardium but also in the underlying myocardium. It occurred exactly at the root of the leaflet. One of the smaller tubercles was cut at three levels. In none of the sections did the tubercle extend into the myocardium. The fibers of the endocardium were merely somewhat separated by the infiltration of large mononuclear wandering cells.

No tubercle bacilli or other organisms were stained in the endocardial tubercles, but tubercle bacilli were noted in other organs.

A large microscopic section of the myocardium showed two very small tubercles lying deep in the cardiac muscle.

This case was one of tuberculosis of the pericardium and myocardium with involvement and erosion of the endocardium. The ulceration was thought to be the source of the generalized miliary tuberculosis.

CASE 6.—A Negro, aged 25, was admitted to the Lincoln Hospital (Durham, N. C.) in a stuporous condition shortly before death, and no adequate history was obtainable. He had a stiff neck, which was painful on motion. Clinical examination of the heart revealed nothing remarkable.

Macroscopic Examination.—Tuberculous meningitis was the immediate cause of death, and there was generalized miliary tuberculosis.

The heart with the adherent pericardium weighed 560 Gm. The heart alone was considerably enlarged. Between the thickened pericardial layers were caseous masses. One of them extended into the right atrium as a mass measuring on section 2 by 1.5 cm. It presented itself as a nipple-like, ulcerated apex on the inside of the atrium above the tricuspid valve (fig. 4). This nodule was the largest of several yellow tubercles which were seen in a group on the inside of the right atrium. All of them seemed to be smooth-surfaced except for the ulceration on the large projection. The endocardium elsewhere, including the valves, appeared normal.

Numerous caseous, scarred and partially calcified lymph nodes surrounded the pulmonary artery and aorta and came in direct contact with the pericardium. No point of ulceration of these nodes into the pericardial cavity was demonstrated, but it was thought that they may previously have ruptured into the pericardium and caused pericardial tuberculosis. In the upper part of the lower lobe of the left lung lay a scar, covered with thickened and depressed pleura and extending 2 cm. into the tissue of the lung. This was thought to be the primary lesion in the body.

Miliary tubercles, measuring from 1 to 2 mm. in diameter and placed from 2 to 5 mm. apart, were uniformly scattered through the lungs. Tubercles of about the same size occurred in the spleen, liver, kidneys and other organs but were spaced farther apart.

Microscopic Examination.—A section of the tissues through the caseous mass (fig. 5) included the two thickened pericardial layers and showed the right ventricle and tricuspid valve on the side of the tubercle on which the coronary artery is found. On the side of the tubercle opposite the coronary artery lay the muscle of the right atrium. Between the pericardial layers just outside the ventricle

and coronary artery were large caseous masses. No cardiac muscle lay external to the main caseous mass. The mass had replaced the muscle of the right atrium and extended into the endocardium. Weigert's elastic tissue stain brought out the prominent elastic component of the endocardium and indicated the course of the latter layer, as shown by the dotted line in figure 5. Thus, the caseous mass lay in part both within and on the endocardium.

No tubercle bacilli were observed in the caseous mass after prolonged search, but they were seen in the lung.

The next case was similar to case 6. An endocardial lesion developed from myocardial and pericardial tuberculosis. However, the endocardium did not appear to be ulcerated, and no generalized miliary

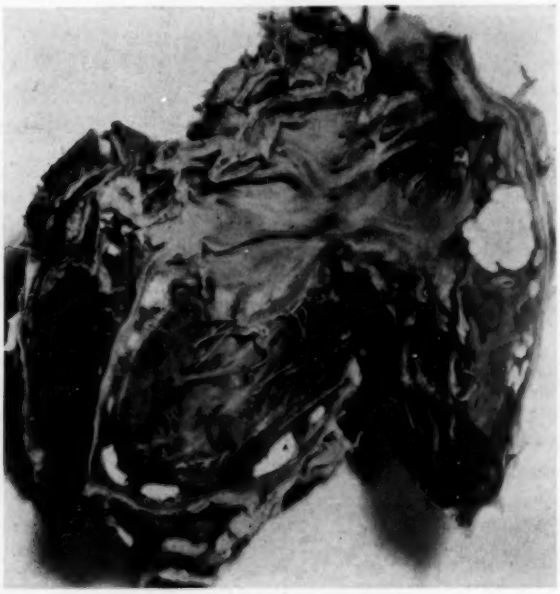

Fig. 4 (case 6).—Pericardial tuberculosis with a caseous mass extending through the wall of the right atrium and involving the endocardium.

tuberculosis was present. It is of interest to note how much endocardial involvement can be present without ulceration.

CASE 7.—*Macroscopic Examination.*—The necropsy was performed at the Baltimore City Hospitals. The organs were those of an adult. The thick parietal pericardium was separated from the heart by caseous material. The heart and pericardium together weighed 600 Gm. Large caseous myocardial nodules formed an almost continuous layer in the ventricular walls. It was thought that pericardial tuberculosis had arisen from caseous mediastinal nodes. No pulmonary, miliary or freshly disseminated tuberculosis was present. The mesenteric nodes showed caseous and fibrous tuberculosis.

The pertinent fact, however, was that the myocardial tuberculous lesions bulged into the cardiac cavities in knobby masses and yet seemed to be everywhere covered

with a smooth inner lining. The caseous masses were prominent in both atria and in the right ventricle. One of them projected 0.5 cm. into the left atrium as a nonulcerated, irregular caseous nodule. The cardiac valves appeared normal.

Microscopic Examination.—An elastic tissue stain of the caseous mass projecting into the left atrium is shown in figure 6. To the right was the mitral valve. The main elastic fibers of the endocardium lay beneath the surface of the mass in several places. They were interrupted in other places. Granulation tissue was abundant on the surface of the elastic band. No endothelial layer over the elastic

Fig. 5 (case 6).—Lantern slide of tissue from the caseous mass in the atrial wall. The dotted line represents the course of the elastic tissue and demonstrates the amount of endocardial involvement; hematoxylin and eosin stain; × 1.7.

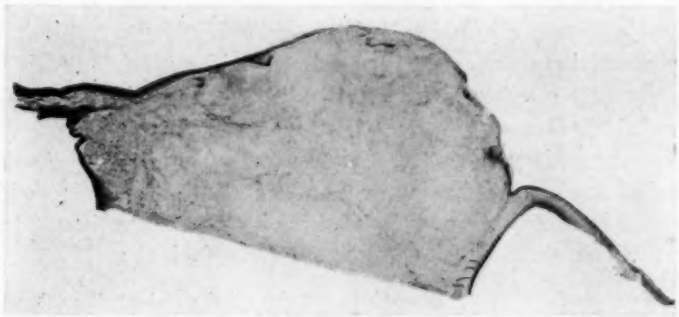

Fig. 6 (case 7).—Myocardial tuberculosis bulging into the left atrium. Grossly, the mass seemed to be covered everywhere with a smooth inner lining. A section treated with Weigert's elastic tissue stain shows a considerable degree of endocardial involvement; × 3.7.

tissue could be seen. Yet on gross examination the nodule appeared to be covered with a smooth lining.

In connection with the first five cases it should be mentioned that through the courtesy of Dr. E. B. Krumbhaar I examined a child's heart in the pathologic museum of the University of Pennsylvania, in which there was a caseous nodule from 3 to 4 mm. in diameter on the atrial surface of the aortic leaflet of the mitral valve about one third of the distance from the ring of the valve to the free border.

DATA FROM THE FILES OF THE JOHNS HOPKINS HOSPITAL

Through the courtesy of Dr. W. G. Mac Callum I examined the index and appropriate protocols of nearly thirteen thousand autopsies performed at the Johns Hopkins Hospital. Reference was made to a number of cases in which tubercles had been observed on the inner lining of the heart and on the heart valves. It was evident that the tubercles were nearly always part of generalized miliary or disseminated tuberculosis. They varied in size from that of the minutest flecks to a diameter of 3 mm. They occurred most frequently on the parietal ventricular endocardium, especially on that of the right ventricle beneath the pulmonary valves. They were situated on papillary muscles and in one instance at the base of a valve, but in no instance were they far out on the leaflet of the valve.

In one case caseous nodules appeared in the wall of the heart of a child of 1 year. Several nodules projected into the right ventricle. There was a good-sized tubercle in the tip of the left auricular appendage. It is possible that in this case there may have been endocardial involvement, as in case *7* already mentioned.

There were no instances of anything like diffuse vegetative tuberculosis or tuberculous endocarditis at the line of closure of the valves. No thrombus formation in connection with the tuberculous lesions was cited.

DATA FROM THE LITERATURE

Endocardial tubercles in generalized miliary tuberculosis [3] were apparently first mentioned by von Recklinghausen [4] in 1859. On the endocardial surface of the ventricles and atria in a man of 20 were about twenty miliary tubercles. They usually projected above the free endocardial surface. The larger portions of the tubercles which he examined microscopically were embedded in the myocardium. In 1879, Weigert [5] made the following statement (translation):

> Miliary tuberculosis of the heart, in particular of the endocardium, is an almost regular occurrence in acute general miliary tuberculosis. If one is in some measure trained to see the nodules and hunts for them in the right place they are observed to be absent only when tubercles of the other organs are scarce. Among ten cases there will perhaps be one in which they are missed. The site of predilection for the tubercles is the right conus arteriosus as far as, and including, the large

3. (*a*) Wagner, E.: Arch. d. Heilk. **2**:574, 1861. (*b*) Rindfleisch, E.: Pathological Histology, London, The New Syndenham Society, 1872, vol. 1, p. 278. (*c*) Letulle: Bull. Soc. anat. de Paris **59**:557, 1874. (*d*) Bonome, A.: Pathologica **3**:481, 1911. (*e*) Stefko, W.: Ztschr. f. Tuberk. **44**:199, 1926. (*f*) Oshima, K.: J. Chosen M. A. (Abstr. Sect.) **23**: 59, 1933.

4. Von Recklinghausen, F.: Virchows Arch. f. path. Anat. **16**:172, 1859.

5. Weigert: Virchows Arch. f. path. Anat. **77**:293, 1879.

papillary muscle. The next most frequent site of occurrence of the tubercles is in the endocardium of the right ventricle, then that of the left ventricle, especially on the septum.

Reichenbach [6] stated that of eighty-five cases of miliary tuberculosis occurring in children the tubercles were seen from the endocardial surface in only 9.4 per cent. I am of the opinion that this percentage is too low, provided a thorough search is made for the tubercles. If all the cases were included in which slight generalized dissemination of the tubercles occurred, the percentage would still be rather low. At the same time, Weigert's estimate of nine out of ten cases is surely too high.

Banquet [7] described and pictured a tubercle in the endocardium of a fetus of 7 months from a tuberculous mother, in which tubercle bacilli in large numbers were stained.

Reinhard [8] described the occurrence of "contact" miliary tubercles. In a case of miliary tuberculosis he observed a tubercle on each of the two papillary muscles of the left ventricle. The two miliary tubercles were so situated that when the heart was active they must have been in contact at times. It seemed to the author that one tubercle must have been implanted from the other. He used this observation as evidence that implantation may occur directly on the free surface of the endocardium from bacilli circulating in the blood.

A number of descriptions of caseous endocardial tubercles occurring as part of generalized miliary tuberculosis and similar to those in cases 1 and 2 of the present series have been given.[9]

Cases similar to case 6 of my series are fairly frequent in the literature.[10] Undoubtedly, in many of the cases of myocardial tuberculosis which have been described it could have been shown that the endocar-

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6. Reichenbach: Ueber Tuberkulose des Herzens im Kindesalter, Dissert., Zurich, 1896; cited by Thorel [1n] (part 1).

7. Banquet, P. H.: L'endocardite tuberculeuse, Thèse de Bordeaux, no. 103, 1898.

8. Reinhard, Hans: Virchows Arch. f. path. Anat. **210**:248, 1912.

9. Schuchardt, K.: Virchows Arch. f. path. Anat. **88**:45, 1882. Thiry, C.: Presse méd. **5**:lxxxiii, 1897. Benda, C.: Deutsche med. Wchnschr. (proceedings) **24**:27, 1898. Sabrazès, J., and Brengues, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **16**: 805, 1899. Nauwerck: München. med. Wchnschr. **52**:976, 1905.

10. von Genersich, A.: Centralbl. f. allg. Path. u. path. Anat. **8**:819, 1897. Fontoynont: Bull. Soc. anat. de Paris **72**:101, 1897. Nattan-Larrier, L.: Bull. Soc. anat. de Paris **72**:460, 1897. Benda, C., and Geissler: Deutsche med. Wchnschr. **31**:1170, 1905. Schwarz, G.: Centralbl. f. allg. Path. u. path. Anat. **16**:261, 1905. Silbergleit, H.: Virchows Arch. f. path. Anat. **179**:301, 1905. Knotte, E.: Ueber einen Fall von schwerer allgemeiner Tuberkulose mit Herz- und Gallenblasentuberkulose, Dissert., Leipzig, 1907; cited by Thorel, C.: Ergebn. d. allg. Path. u. path. Anat. **14** (pt. 2): 454, 1910. Dillon, E. S.: M. Clin. North America **10**:253, 1926. Gouley, B. A.; Bellet, S., and McMillan, T. H.: Arch. Int. Med. **51**:244, 1933.

dium was involved, as in case 7, if elastic tissue staining of the sections had been attempted. Usually pericardial tuberculosis was present when there was extension from a myocardial mass into the endocardium. Often the ulcerated endocardial projection was interpreted as the starting-point of generalized miliary tuberculosis which was not infrequently noted. In some instances the caseous endocardial mass grew into and involved one of the cardiac valves. Fränkel [11] reported the rupture of a caseous lymph node directly into the right atrium in a case of miliary tuberculosis. Secousse, Caussimon and Giraud [12] reported an interesting case of tuberculous abscesses of the endocardium. In the apical portion of the right ventricle were at least two well encapsulated abscesses as large as chestnuts and several smaller ones, all of which were stated to be entirely in and on the endocardium and not in the myocardium. The pus from one of these pockets contained many tubercle bacilli. Inoculation of guinea-pigs with the pus gave positive reactions. Apparently the abscesses were not connected with the cavity of the heart at any point. The myocardium and pericardium were said to appear normal macroscopically.

Polypoid Tubercles.—Pedunculated and polypoid endocardial tubercles were not noted in the cases of the present series, but they have been reported in the literature.[13] Perhaps the best account of this type is that by Schultze.[14] In the heart of a boy who died of generalized miliary tuberculosis, he noted on the anterior papillary muscle of the left ventricle, 3 mm. from the apex, a polypoid structure attached to the muscle by a narrow base. The projecting structure was 7 mm. long. It measured 4 mm. in diameter at the broadest part and only 1.5 mm. at the point at which it joined the heart. The free end was directed toward the aorta and ended in a blunt area which appeared eroded. Many tubercle bacilli were stained. The structure was apparently similar to that of tubercles in the pulmonary artery described recently by Gross.[15] A pedunculated tubercle of the endocardium, not a part of generalized miliary tuberculosis but arising from the extension inward of myocardial or pericardial tuberculosis, was reported by Püschmann.[16]

Tubercles and Cardiac Function.—Only three instances were noted in which tuberculous nodules of the valves could have had significance

11. Fränkel, E.: München. med. Wchnschr. **52**:1417, 1905.

12. Secousse, H.; Caussimon, J., and Giraud, D.: J. de méd. de Bordeaux **102**: 595, 1925.

13. Wagner [3a] Bosch, L. C.: München. med. Wchnschr. **57**:1093, 1910. Hübschmann, P.: ibid. **59**:841, 1912. Dressler, W.: Frankfurt. Ztschr. f. Path. **26**:401, 1922.

14. Schultze, W. H.: Centralbl. f. allg. Path. u. path. Anat. **17**:305, 1906.

15. Gross, P.: Am. J. Path. **9**:17, 1933.

16. Püschmann, M.: Centralbl. f. allg. Path. u. path. Anat. **8**:818, 1896.

in cardiac function. In Hueter's [17] case there was perforation of one of the leaflets of the tricuspid valve by a tuberculous process arising in the myocardium. In Soli's [18] case a caseous tubercle as large as a pigeon's egg lay partly in the myocardium and partly in the tricuspid valve. The chorda tendinea of a papillary muscle passed directly through the nodule. Laubry and Soulié [19] presented a case with a history of polyarthritis and attacks of cardiac decompensation for three years. The clinical diagnosis was rheumatic heart disease. At autopsy a tubercle about 1 cm. in diameter was seen within the substance of the aortic leaflet of the mitral valve, obstructing the lumen. The endocardium on both the auricular and the ventricular aspect of the nodule seemed normal. On section the nodule was caseous with a purulent center, and tubercle bacilli were demonstrated in a smear. Miliary tuberculosis was absent, but other evidences of tuberculosis were noted in the body. The mitral valve showed no evidence of active or healed rheumatic infection. No myocardial tubercles were observed.

Tuberculous Thrombi.—Much material was found in the literature concerning tuberculous thrombi of the heart.[20] It was difficult to obtain a clear idea of the cases which were reported because of the inadequacy of the descriptions and the lack of illustrations. Many of the "thrombi" were probably tubercles. In some cases the suggestion was made that tubercle bacilli had become caught in a thrombus and had transformed it into tuberculous tissue. Moser [21] noted what he termed a thrombus at the apex of the left ventricle in a man of 53 who had a cavity in one lung and tuberculosis of the epididymis and seminal vesicles. The cardiac thrombus was organizing, but undissolved fibrin was enclosed in the meshes. Tubercle bacilli occurred in the thrombus, usually in giant cells. Marchiafava [22] described numerous grayish-yellow elevations on the mitral valve. Histologically these nodules showed granulation tissue, surmounted by what was said to be thrombotic material, in which there were enormous numbers of tubercle bacilli. No true tubercles or giant cells were seen. The description was inadequate, and there were no illustrations.

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17. Hueter: München. med. Wchnschr. **52**:431, 1905.

18. Soli, U.: Pathologica **2**:243, 1910.

19. Laubry, C., and Soulié, P.: Bull. et mém. Soc. d. hôp. de Paris **48**:567, 1932.

20. Birch-Hirschfeld, F. V.: Centralbl. f. allg. Path. u. path. Anat. **2**:807, 1891; Deutsche med. Wchnschr. **18**:267, 1892. Kotlar, E.: Prag. med. Wchnschr. **19**:78, 1894. Warthin, A. S.: M. News **74**:453, 1899. Tarozzi, G.: Centralbl. f. allg. Path. u. path. Anat. **14**:700, 1903.

21. Moser, A.: M. & S. Rep. Boston City Hosp. (ser. 11) 1900, p. 194.

22. Marchiafava, E.: Boll. d. clin. **35**:137, 1918.

Tuberculous Endocarditis.—A thorough search for reports of cases of tuberculous endocarditis which were analogous to those of rheumatic and bacterial endocarditis showed few which stood critical analysis. To be acceptable cases should meet certain standards, which may be summarized as follows:

1. Microscopic sections of the lesions should show a tissue reaction consistent with one of the various appearances of tuberculous lesions.

2. Tubercle bacilli preferably should be stained in the endocardial lesions themselves.

3. Demonstration of bacilli from the blood stream should not be accepted as proof that the endocardial lesions are tuberculous. Even the production of tuberculosis in a guinea-pig by the injection of material from the lesion itself cannot be considered conclusive. The blood bathes the lesion, and there may be blood vessels in the lesion. In both instances, the bacilli may be derived from the blood. The presence of widespread tuberculosis elsewhere in the body is not proof that endocardial lesions are also tuberculous.

4. Other causes for the endocardial lesions should be excluded. It should be impossible to stain pyogenic organisms in the lesions or to cultivate them from material from the lesions. Sections of the myocardium should always be studied to determine the absence of Aschoff bodies.

The consideration of tuberculous endocarditis has a prominent place in a treatise by Pic and Morenas, entitled "La tuberculose cardio-vasculaire." [1d] A long bibliography is given of the reports of tuberculous endocarditis, mostly by French authors. Morphologically the lesions in many of these cases strongly suggest rheumatic endocarditis. In most instances, the decision that the lesions were tuberculous rested on the positive results of inoculation of guinea-pigs or on the cultivation of acid-fast organisms from the blood stream. The possible errors in proof of this kind are apparent. In addition, Wilson [23] in a recent monograph emphasized the many pitfalls in the technic of diagnosis of tuberculous bacillemia.

Pic and Morenas concluded in another study [24] (translation):

> In contrast to lesions of the endocardium which are anatomically demonstrable as tuberculous (with tubercles), rare manifestations and without clinical interest, there exists a tuberculous endocarditis. The latter condition is inflammatory in its behavior, has no anatomic specificity, occurs often, is rarely met with in the active stage but frequently is manifested by sclerosis of the parietal endocardium or of the valves. This form of endocarditis occurs in adults and may be suspected

23. Wilson, G. S..: Tuberculous Bacillaemia, Medical Research Council, Spec. Rep. Ser. 182, London, His Majesty's Stationery Office, 1933.

24. Pic, A., and Morenas, L.: J. de méd. de Lyon **8**:185, 1927.

clinically at times; its diagnosis, unfortunately difficult, is not without practical interest. It is more frequent in children. It constitutes, with rheumatic endocarditis, the cause of many valvular cardiopathies discovered in the adult, which are primary in appearance—in particular, the mitral stenoses said to be congenital.

With these conclusions I heartily disagree, and evidence against them will be presented later.

About twenty-four cases of tuberculous endocarditis were found in the literature which either did not stand critical analysis or were so incompletely described that one could tell little about them.[25]

Only the cases of Benda,[26] Witte,[27] Marchiafava [22] and Meek [28] could be accepted as approximations of true tuberculous endocarditis in the sense of a diffuse involvement of the valves at the line of closure, analogous to rheumatic and bacterial involvement.

Benda's case was really one of a tuberculous process of the aortic valve continuous with epicardial tubercles, and the involvement was not diffuse.

Marchiafava's case has already been mentioned. There was said to have been a thrombus formation in connection with the lesions, but the description was not thoroughly convincing.

In Witte's case the "posterior lateral" leaflet of the mitral valve, where it met the medial side of the aortic leaflet, showed a thickening as great as 7 mm. and about the size of a 5 pfennig piece, which reached

25. Lancereaux and Lackerbauer: Atlas d'anatomie pathologique, Paris, Victor Masson et fils, 1871, p. 218; plate 22. Perroud, P.: Lyon méd. **19**:12, 1875. Heller: Berl. klin. Wchnschr **23**:875, 1887; Centralbl. f. allg. Path. u. path. Anat. **1**: 303, 1887. Tripier, R.: Arch. de méd. expér. et d'anat. path. **2**:360, 1890. Londe, P., and Petit, R.: Arch. gén. de méd. **173**:94, 1894. Michaelis, M.: Deutsche med. Wchnschr. **21**:147, 1895. Leyden, E.: Deutsche med. Wchnschr. **22**:19, 1896. Étienne, G.: Arch. de méd. expér. et d'anat. path. **10**:146, 1898. Aguerre, J. A.: Bull. et mém. Soc. anat. de Paris **74**:434, 1899. Poncet, A.: Lyon méd. **99**:72, 1902. Braillon, L., and Jousset, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **20**:809, 1903. Ferrand, J., and Rathery, F.: Bull. et mém. Soc. méd. d. hôp. de Paris **20**:427, 1903. Barbier, H.: Bull. et mém. Soc. méd. d. hôp. de Paris **22**: 271, 1905; Bull. et mém. Soc. méd. d. hôp. de Paris **42**:422, 1918; Bull. et mém. Soc. méd. d. hôp. de Paris **42**:1159, 1918. Sorgo, J., and Suesz, E.: Wien. klin. Wchnschr. **19**:176, 1906. Landouzy, L., and Leaderich, L.: Presse méd. **16**:481, 1908; Rev. de méd., Paris **28**:765, 1908. Lortat-Jacob, L., and Sabareanu, G.: Presse méd. **16**:633, 1908; Bull. et mém. Soc. anat. de Paris **79**:249, 1904. Landouzy, L., and Gougerot, H.: Presse méd. **16**:713, 1908. Bouchara, J. B.: Contribution à l'étude de l'endocardite tuberculeuse, Inaug. Dissert. Algeria; cited in Zentralbl. f. Herz-u. Gefässkr. **6**:41, 1912. Ardin-Delteil, P.; Raynaud, M.; Coudray, M., and Pelissier, A.: Bull. méd. de l'Algérie **23**:627, 1912. Braillon, L.: Bull. et mém. Soc. méd. d. hôp. de Paris **42**:668, 1918.

26. Benda, C.: Berl. klin. Wchnschr. **36**:597, 1899.

27. Witte, J.: Beitr. z. path. Anat. u. z. allg. Path. **36**:192, 1904.

28. Meek, W. O.: Proc. Roy. Soc. Med. **1**:116, 1908.

from the base of the valve to the line of closure. This thickenning consisted of dry, compact caseous masses and was covered on the free surface with caseous nodules the size of the head of a pin. No old valvular lesion was present; no thrombus overlay the lesion, and there was no mixed infection. Great numbers of tubercle bacilli were noted within the lesion. The point of origin was given as within the tissue of the valve where the masses of bacilli lay, and it was thought that the origin from a surface colonization on the mitral valve could be excluded. The origin of the whole process seemed to be a tuberculous lesion of the hip which had led to a chronic and subacute miliary tuberculosis.

The most convincing of all these cases was one of the two reported by Meek.[28] This case was possibly "a true example of a vegetative endocarditis due to the tubercle bacillus." In a boy of 16 during the period of almost two months prior to his death "a murmur was audible over the cardiac area. The characters were those of a haemic bruit." At autopsy generalized miliary tuberculosis was noted. There was a small cavity in the upper lobe of the right lung. The heart weighed 12 ounces (340.2 Gm.).

> On the ventricular surface of the aortic, and on the auricular surface of the mitral valve segments were a row of recent small vegetations. They were regularly disposed on each of the cusps and were situated a short distance from the free edges of the segments. In the case of the aortic valve the vegetations were exceedingly minute and white in colour. On the mitral cusps they were somewhat larger, the largest being the size of a No. 5 shot, and were light brown in colour. In both situations they were friable and soft. There was no evident destruction of valve tissue and no signs of pre-existing valvular disease. . . . The valves on the right side of the heart were healthy.

Microscopic examination showed necrotic areas and enormous numbers of tubercle bacilli. No other organisms were seen in section or in the cultures of material from the splenic pulp. Several good photographs of microscopic preparations were given, but there was no photograph of the macroscopic appearance of the lesion.

While the general description suggests a case of rheumatism, the friability of the vegetations and the presence of tubercle bacilli dismiss that interpretation. The absence of the usual pyogenic organisms also seemed clear.

Other Aspects of Endocardial Tuberculosis.—Reports of cases of spontaneous tuberculous endocarditis in animals were few, and most of them were open to question.[29] However, in dogs tuberculous ulcerated endocarditis secondary to tuberculosis of the myocardium has apparently occurred.

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29. Pallaski, G.: Centralbl. f. allg. Path. u. path. Anat. **55**:69, 1932. Nieberle, K.: Ergebn. d. allg. Path. u. path. Anat. **25**:648 and 785, 1931; **26**:743, 1932.

Several reports have been made of experimental tuberculous endocarditis in animals.[30] Apparently, tubercles of the endocardium have been produced by endocardial trauma together with injections of bacilli. However, even in these cases there was not a diffuse involvement at the line of closure of the valves.

"Toxic" tuberculous endocarditis has been the subject of several articles.[31] In a recent study, de Vecchi [2] stressed the presence of endocarditis demonstrable histologically on valves which to the naked eye appeared normal. He noted scattered lymphocytic infiltrations and endothelial desquamation in two cases of miliary tuberculosis and an even greater reaction of a similar nature in a case of "acinonodular pulmonary tuberculosis with nodular tuberculosis of the liver and spleen." The photomicrograph of the cardiac lesion in the last case strongly suggests a tuberculous lesion. One wonders whether tubercle bacilli could not have been stained in this lesion. As to etiology, the writer expressed the belief that a toxic action on the part of the tuberculous process may cause the lesions. That such a toxic action, as in cases of long-standing and widespread pulmonary tuberculosis, is not especially significant will be indicated later.

COMMENT

Definition of Endocardium.—For the purposes of this study the endocardium was defined as the endothelial layer lining the entire inside of the heart, including the valves and the underlying connective tissue, which in some places includes smooth muscle. This layer consists of all the tissue lining the inside of the cardiac muscle. Since the cardiac valves contain no cardiac muscle, any lesion involving them, whether on the surface or embedded in their substance, is an endocardial lesion.

Origin of Endocardial Tubercles.—Benda [26] differentiated sharply between "organ" tubercles and intimal tubercles in the cardiovascular system. The "organ" tubercle, in the case of the heart, arises in the myocardium and extends into the endocardium, while the true endocardial tubercle arises on or in the endocardium. Benda said that "organ" tubercles often were visible on the inside. He claimed that the sure way

30. Michaelis, M., and Blum, S.: Deutsche med. Wchnschr. **24**: 550, 1898. Bernard, L., and Salomon, M.: Rev. de méd., Paris **25**:49, 1905. de Vecchi, B.: Deutsche med. Wchnschr. **31**:764, 1905 (abstr.); Centralbl. f. Bakt. **36**:550, 1905. Fulci, F.: Beitr. z. path. Anat. u. z. allg. Path. **44**:390, 1908. Lissauer, M.: Centralbl. f. allg. Path. u. path. Anat. **23**:243, 1912. Mencarelli, L.: L'endocardite sperimentale da bacilli della tuberculosi, Cuore e circolaz. **14**:140, 1930.

31. Hanot, V.: Arch. gén. de méd. **171**:727, 1893, Teissier, J.: Les lésions de l'endocarde chez les tuberculeux, Paris, J. B. Baillière et fils, 1894; cited by Schwalbe: Deutsche med. Wchnschr. **21**:89, 1895. Mencarelli, L.: Cuore e circolaz. **14**:273 (June) 1930.

of differentiating the two types of tubercles was by the aid of elastic tissue stains. According to him, the fresh vascular focus (in contradistinction to the "organ" focus) lay inside the innermost elastic lamella. "They may, toward the lumen, still be covered with an endothelial layer."

This relationship to the endocardial elastic tissue has been accepted by subsequent writers as of prime significance in determining the origin of the tubercles.[32] The differential elastic tissue stains make such striking histologic pictures that one naturally thinks that the elastic tissue must act as a barrier. It is not clear, however, that elastic tissue staining is a differential point. The presence or absence of blood vessels in the endocardium would seem to be much more important. There is still a difference of opinion as to whether there are blood vessels in the normal cardiac valves.[33] Apparently, little work has been done on this problem with regard to the parietal endocardium (Benninghoff[34]). The author's rather limited observations indicated that in ordinary sections no capillaries could be found in the parietal endocardium. If this is so, it would be about as difficult for tubercle bacilli to reach any part of the endocardium from the myocardial side as from the inside of the heart. But conceivably tubercle bacilli could pass into tissue spaces, possibly with the aid of large mononuclear cells, and the absence of capillaries would not be a limiting factor. Wherever the endocardium has elastic sheets, the latter tissue may conceivably act as a barrier. If the valves are avascular, as many workers now declare, a tubercle on a valve uninjured by a previously existing inflammatory process must have arrived there directly from the circulating blood in the heart cavity.

While the staining of elastic tissue is thus not clearly a deciding aid in determining the origin of a tubercle, it is of the greatest help in following the course of the endocardium into the substance of a caseous mass, as was shown in several of my cases.

Convincing evidence that tubercles can arise directly on the inside of the heart is found in the case of Reinhard,[8] in which "contact" tubercles were noted on adjacent papillary muscles, and the assumption seems fair that one arose from the other by implantation.

As demonstrated in several of the cases of miliary tuberculosis in the present series, the number of myocardial tubercles was surprisingly small in comparison with the number of endocardial tubercles. This fact itself suggests that endocardial tubercles may arise directly from the blood of the cardiac cavities.

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32. Stark, J. R.: J. Lab. & Clin. Med. **2**:731, 1917.

33. Bayne-Jones, S.: Am. J. Anat. **21**:449, 1917. Gross, L., and Kugel, M. A.: Am. J. Path. **7**:467, 1931. Dow, D. R., and Harper, W. F.: J. Anat. **66**:610, 1932.

34. Benninghoff, A., in von Möllendorf, W.: Handbuch der mikroscopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, pt. 1, p. 162.

Tuberculous Endocarditis.—It seems strange, at first thought, that tuberculous endocarditis of the valves is not more frequent. Surely tuberculous bacillemia is not rare, judging from the occurrence of isolated lesions, such as those of the kidney, which could arise only via the blood stream. One might expect valvular endocarditis as a result. Why do not organisms become implanted on the valves and produce endocarditis, as occurs not infrequently with several of the pyogenic organisms? Meek [28] reported the only satisfying description of a case in which this actually occurred. Because of the exceptional rarity of this case, probably a contributing factor should be invoked, for example, the development of tuberculous bacillemia coincident with the onset of fresh rheumatic endocarditis.

In the great majority of cases, it is apparent that the endocardial tuberculous process occurs not at the line of closure but here and there over the inside of the heart.

Opie [35] wrote:

> I assume that few tubercle bacilli stick to the surface of normal endothelium. This, however, gives no satisfactory explanation of the infrequency of tubercles in situations, as on the heart valves, where pyogenic cocci find lodgment.

Rich [36] wrote:

> In the case of the tubercle bacillus I think that one of the important reasons why it does not produce endocarditis may be its extremely slow growth in comparison with that of the pyogenic bacteria. If a bacillus lodges on a valve it will probably be dislodged before it has proliferated enough to produce damage to the tissue. At least, that is a possible factor. It certainly explains why a tubercle bacillus slipping from the blood into the meninges does not promptly produce meningitis, in contrast to the ease with which a single organism of the more rapidly growing bacteria produces myriads in a few hours.

Usually, the tubercle bacillus is dealt with by the large mononuclear cells. The small number of these reticulo-endothelial cells on the valves of the heart and endocardium may help to explain the infrequency of tuberculous lesions here as compared with their abundance in the liver and spleen.

It is preferable to give a tuberculous lesion of the endocardium the term endocardial tuberculosis rather than tuberculous endocarditis, unless the inflammatory reaction is outstanding. Articles dealing with these cases are entitled "tuberculous endocarditis" when only isolated endocardial tubercles were seen. Even in Meek's case of diffuse valvular lesions, necrosis was the important tissue reaction so far as one can learn from the description. The question hinges on the varying conceptions of inflammation. If the mobilization or exudation of large mono-

35. Opie, E.: Personal communication.

36. Rich, A.: Personal communication.

nuclear cells is a part of inflammation, even most of the instances of isolated endocardial tubercles may be called tuberculous endocarditis, unless necrosis is the only factor. If, on the other hand, the term inflammation is restricted, only the instances in which the more acute types of inflammatory reaction are present should be termed tuberculous endocarditis. The safest plan, probably, is to locate the tuberculous endocardial process anatomically and use the term endocarditis sparingly.

Thrombus Formation.—The absence of thrombus formation in connection with the lesions in the cases presented was particularly noted. Even when the endothelial layer could not be followed over the tubercle and in the presence of ulceration, no thrombosis occurred. This fact accounts for the inconspicuous character of the endocardial tubercles, for were they lesions produced by pyogenic organisms, luxuriant thrombotic vegetations would undoubtedly have occurred.

Failure to Recognize "Tuberculous Endocarditis."—To test the statement of Pic and Morenas [24] that valvular endocarditis of tuberculous origin is a fairly common occurrence, even detectable clinically at times, the material from six hundred consecutive autopsies done at Duke Hospital was restudied. Although in no case had an anatomic diagnosis of such a form of endocarditis been made, it was thought that the possibility of a tuberculous origin may not have been in mind when the cases were originally studied. It was, of course, realized that, even if no cases were found, one would not be justified in assuming that the condition might not exist in another locality or that it might not be demonstrated when a larger number of cases was examined. However, the high incidence of tuberculosis among the Negro population in North Carolina and the frequency with which patients with endocarditis are referred to a teaching hospital made a survey of this kind seem valuable.

Thirty-seven cases of valvular endocarditis were found in the six hundred autopsies. Not included were the instances of slight sclerosis and lipoid infiltration and even of stiffening of the bases of the mitral and aortic leaflets, commonly associated with arteriosclerosis elsewhere in the body but not interfering with the free play of the valves.

The thirty-seven cases were divided as follows:

Syphilis of the aortic valve	11
(2 with superimposed bacterial endocarditis)	
Bacterial infection	13
(8 with underlying endocardial lesion)	
Rheumatic endocarditis with Aschoff bodies in the myocardium	3
Unclassified	10
Total	37

In the cases of bacterial endocarditis, the organism involved had been grown from cultures of the blood or of material from the vegetations or

had been stained in sections of the vegetations. The organisms included staphylococci, streptococci, pneumococci, gonococci and also gram-positive cocci not identified culturally. Search for tubercle bacilli in microscopic sections of the vegetations of six of the cases showed the absence of acid-fast organisms, while a control section stained simultaneously and known to contain tubercle bacilli showed them in large numbers. This search was made to see whether tubercle bacilli might not be present in addition to the nonacid-fast organisms, in the form of a mixed infection.

It is to be noted that eight of the cases of bacterial endocarditis showed an underlying, older endocardial lesion. If they are added to the ten unclassified cases, there were eighteen cases in which the cause of the lesions did not seem perfectly clear. Possibly among them a case of diffuse valvular endocarditis of tuberculous origin might be found.

Search for tubercle bacilli in sections of the involved valves in twelve of the eighteen cases failed to show acid-fast organisms, while the control sections showed many. In none of the sections of the involved valves were there tubercles, caseation or tissue suggesting a tuberculous process.

When the other organs in the eighteen cases were examined thoroughly for evidences of tuberculous infection, the following data were obtained:

1. No large or widespread tuberculous process was demonstrable in any of the organs in these cases.

2. In one case two caseous, partly calcified tubercles in the liver, each measuring 2 mm. in diameter, were shown.

3. In five of the cases pleural adhesions appeared, which may indicate a previously existing tuberculous infection. In two of the cases there were apical scars, rather good evidence of a preexistent tuberculous infection.

It is clear, then, that there was no correlation between endocarditis in these cases and extensive or widespread tuberculosis elsewhere in the body and that no more evidence of small healed tuberculous foci was seen than would have been noted in similar autopsy material selected at random.

When the organs in the eighteen cases were examined with the idea that the endocardial changes were due to rheumatic heart disease, the following data were secured:

1. In ten cases rather definite evidence of preexisting rheumatic heart disease was present, not only in the valvular lesions consistent with rheumatic heart disease but in changes elsewhere characteristic of healed rheumatic cardiac disease, such as perivascular scarring in the myocardium, a rheumatic atrial patch or pericardial adhesions.

2. In seven of the remaining eight cases healed valvular endocardial changes alone were shown, consistent with a healed rheumatic process. In one case, in which were noted the two minute hepatic tubercles already referred to, the heart showed stiffening of the aortic leaflets from the base to the free edge and minute scattered, calcified foci. The mitral valve seemed normal. There was a healed lesion, but whether it was of tuberculous, arteriosclerotic or other origin could not be stated.

In brief, no case of diffuse tuberculous endocarditis of the cardiac valves could be found. Cases of healed valvular disease in which the causative factor was not clear could be explained in better ways than by attributing to the lesion a tuberculous origin.

Toxic Tuberculous Endocardial Sclerosis.—The statement of Pic and Morenas that there are generalized sclerosis and increased white opacity of the parietal and valvular endocardium in association with widespread tuberculosis elsewhere is not substantiated by the following study.

The hearts of thirty-two patients in whom tuberculosis was the chief lesion were examined. There were six with fibroid pulmonary tuberculosis with cavities, four with chronic pericardial tuberculosis and four with peritoneal tuberculosis. The lesions represented long-standing, large tuberculous processes sufficient to produce an effect on the endocardium if such an effect could be produced. Control studies were made on the hearts of a similar number of patients in whom evidences of tuberculosis were insignificant. The control group included patients with carcinoma, diseases of the blood, syphilis, acute and chronic nephritis, generalized arteriosclerosis, numerous infectious diseases, etc.

In brief, all the hearts, with the exception of those to be mentioned later, showed the following normal characteristics: (1) a slight white opacity of the endocardium of the right ventricle just beneath the pulmonic valves, (2) a white opacity of the entire endocardial surface of the left atrium with reddish-brown underlying tissue showing through in only one or two places, (3) a nodular thickening to palpation of the free border of the mitral valve, usually in connection with the insertion of the chordae tendineae, (4) white opacities near the tips of the papillary muscles and (5) a rather conspicuous white opacity beneath the aortic valve overlying the membranous part of the interventricular septum but also extending downward a short distance.

These normal conditions were present in the hearts of patients with widespread tuberculosis to the same extent as in those of patients in whom the tuberculous process was insignificant or in whom no such process could be demonstrated. There was no increase in the white opacity on the inside of the chambers of the heart with increase in age. The nodular sensation to palpation of the free border of the mitral valve

was possibly more pronounced in the hearts of persons in the fifth to the seventh decades of life than in those of the first and second decades.

In five types of nontuberculous processes rather diffuse sclerosis of the parietal endocardium could be seen: (1) on the wall of the left ventricle beneath an incompetent syphilitic aortic valve, (2) on the wall of the left atrium, especially in the region of the atrial patch but also more diffusely, and on the papillary muscles in cases of rheumatic endocarditis, (3) overlying myocardial scars, as in cardiac infarction, (4) at the pulmonary conus in a case of congenital heart disease in which there were stenosis of the pulmonary conus and defects in the interventricular and interatrial septums and (5) lining the chambers of the heart, which showed marked dilatation and had probably been dilated for a long time.

It seems probable that the authors who mentioned diffuse sclerosis of the endocardium in cases of tuberculosis were describing the appearance of normal hearts.

SUMMARY AND CONCLUSIONS

Endocardial tuberculosis is not uncommonly encountered at necropsy, most frequently as a part of generalized miliary or disseminated tuberculosis. Scattered tubercles from microscopic size to a diameter of 3 or 4 mm. may occur in any part of the endocardium, including the valves. They probably arise by implantation, through the coronary arteries and directly from the blood of the heart. Rarely they may be polypoid or pedunculated.

Endocardial tuberculosis may also develop from the extension inward of pericardial and myocardial caseous masses, which may ulcerate and produce generalized tuberculosis. With staining for elastic tissue it can be shown that a myocardial tuberculous process bulging into the cavity of the heart but apparently covered with a smooth endocardial surface is in some cases really invading the endocardium.

A convincing report of tuberculous endocarditis as a diffuse process at the line of closure of the valves, somewhat analogous to rheumatic and pyogenic endocarditis, has occurred in the literature possibly once. In general, however, tuberculosis has no especial affinity for the line of closure and does not produce thrombotic vegetations.

Endocardial tuberculosis may interfere with cardiac function in the rare instances in which caseous nodules involve the valves.

Sclerosis of the endocardium and healed fibrous or calcified valvular lesions noted at autopsy were not shown to be due to the toxic action of a tuberculous process elsewhere in the body.

RENAL CHANGES FOLLOWING BILIARY OBSTRUCTION, DECOMPRESSION AND OPERATION ON THE BILIARY TRACT

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In recent years attention has been directed toward certain terminal syndromes which may occur in patients with extensive hepatic disease or following operations on the biliary passages. One of the syndromes is characterized by manifestations of insufficiency of renal function, instances of which have been reported by Stäheli,[1] LeNoir, Richet and Jacquelin,[2] Grauhan,[3] Walters and Parham,[4] Laqua,[5] Furtwaengler,[6] Zaffagnini,[7] Dourmashkin,[8] Fitz-Hugh,[9] Barker,[10] Lederer [11] and Heyd.[12] It was noted that reflex suppression of the functional activity of the kidneys may follow surgical manipulation of the biliary passages. Helwig and Schutz [13] observed several patients with chronic cholecystitis and apparently normal renal function in whom following operation profound uremia developed. Autopsy revealed marked necrosis of the hepatic parenchyma and of the epithelium of the renal tubules with focal hemorrhages and patchy areas of leukocytic infiltration; in no instance did the kidneys present the appearance of biliary nephrosis. Many clinical observations have been made on this relationship, and

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1. Stäheli, E.: Beitr. z. klin. Chir. **123**:103, 1921.
2. LeNoir, P.; Richet, C., and Jacquelin, A.: Ann. de méd. **9**:225, 1921.
3. Grauhan: Zentralbl. f. Chir. **49**:1772, 1922; Arch. f. klin. Chir. **133**:267, 1924.
4. Walters, W., and Parham, D.: Surg., Gynec. & Obst. **35**:605, 1922.
5. Laqua, K.: Beitr. z. klin. Chir. **129**:382, 1923
6. Furtwaengler, A.: Krankheitsforschung **4**:349, 1927.
7. Zaffagnini, A.: Arch. ital. di urol. **4**:161, 1927.
8. Dourmashkin, R. L.: J. A. M. A. **90**:908, 1928.
9. Fitz-Hugh, T.: M. Clin. North America **12**:1101, 1929.
10. Barker, L. F.: M. Clin. North America **14**:261, 1930.
11. Lederer, K.: Wien. Arch. f. inn. Med. **20**:143, 1930.
12. Heyd, C. G.: Am. J. Obst. & Gynec. **19**:203, 1930; J. A. M. A. **97**:1847, 1931; Surg., Gynec. & Obst. **57**:407, 1933.
13. Helwig, F. C., and Schutz, C. B.: Surg., Gynec. & Obst. **55**:570, 1932.

renal functional insufficiency is regarded among others (Stanton [14]) as a serious postoperative complication of surgical manipulation of the biliary tract, yet relatively little information is available regarding the morphologic basis for this phenomenon.

The present study is concerned with renal lesions occurring in patients with various lesions of the liver and biliary tract, some of whom were subjected to operative procedures on the biliary passages.[15] The cases were divided, on an etiologic basis, into four groups for purposes of comparison: (1) twenty-three fatal cases of primary carcinoma of the head of the pancreas with complete and permanent obstruction to the common bile duct; (2) thirteen cases of primary carcinoma of the head of the pancreas completely obstructing the common bile duct, in which death followed surgical decompression of the biliary system; (3) seventeen cases of calculous obstruction with jaundice, in which death followed surgical decompression of the biliary system, and (4) twelve cases of calculous cholecystitis without jaundice, in which death followed operative procedures on the biliary passages. Owing to the fact that primary pancreatic carcinoma usually develops in elderly persons with preexisting renal damage, usually of the senile arteriosclerotic type, the latter type of lesion was noted frequently; since its morphology is well understood it will be referred to only briefly subsequently.

OBSERVATIONS ON GROUP 1

Excellent descriptions of "bile nephrosis" or "cholemic nephrosis" occurring with various types of clinical jaundice were reported by several early observers (Frerichs,[16] Legg [17] and Quincke [18]) and, more recently, by Haessler, Rous and Broun [19] and Wilbur.[20] There have been relatively few attempts, however, to investigate the renal changes associated solely with complete and permanent obstruction of the common bile duct. In the majority of our cases of one or two months' duration the kidneys were of average consistency, smooth and of normal size or only slightly enlarged. In the earlier stages the external markings were well maintained, and the surface was stained diffusely yellow, presenting a peculiar mustard-like cast which turned green on standing. When sectioned the cortex was slightly swollen; the cut edges were everted and the striations accentuated by green stripes traversing the pyramids; these stripes showed the deepest color midway between the apex and the base. Later the cortical tissue varied in color

14. Stanton, E. M.: Am. J. Surg. **8**:1026, 1930.

15. Dr. Stanley P. Reimann, Director of the Lankenau Hospital Research Institute, gave us the opportunity to study cases of this type which occurred in that institution.

16. Frerichs, F. T.: Klinik der Leberkrankheiten, Brunswick, Friedrich Vieweg und Sohn, 1858, vol. 1, p. 107.

17. Legg, J. W.: On the Bile, Jaundice and Bilious Diseases, New York, D. Appleton and Company, 1880, p. 359.

18. Quincke, H.: Virchows Arch. f. path. Anat. **95**:139, 1884

19. Haessler, H.; Rous, P., and Broun, G. O.: J. Exper. Med. **35**:533, 1922.

20. Wilbur, D. L.: Arch. Path. **18**:157, 1934.

from dark green ocher to a deep olive green, presenting the appearance of the so-called grass-green kidney. The surface was stippled by a few dark green convoluted tubules, and the inner layer of the capsule had a golden yellow appearance, due to pigment within the lymphatics. Prominent green and occasional black lines streaked the pyramids, and dark brown or green granules were visible grossly within the tubules. Microscopic examination showed pigment granules of varying size situated both extra-cellularly and within the renal epithelial cells in

Fig. 1.—Photomicrograph (× 125) of a frozen section fixed in solution of formaldehyde, showing pigmentation of the kidney due to obstruction of the common bile duct by pancreatic carcinoma. To the right of the center of the field are a glomerulus and the corresponding proximal convoluted tubule, the pigmented epithelial lining of which is loosened and drawn into the capsular space.

fresh scrapings from the cut surface. This pigmentation can be demonstrated much more satisfactorily in fresh sections or in frozen ones fixed in solution of formaldehyde unstained or lightly colored with eosin or methylene blue. In the preparation of routine paraffin sections the pigment may be largely dissolved or washed away. The interstitial tissue in some instances showed local or generalized hyperemia, edema and slight iron pigmentation, but usually no bilirubin

was recognizable except for a slight brownish discoloration of the tissues due perhaps to postmortem staining of the blood and lymphatic vessels. The glomeruli, as a rule, were entirely free from bilirubin, although bile casts were occasionally observed extending uninterruptedly from the proximal portion of the tubule directly into the capsular space, where fragments of these casts were separated and lying free. It was likewise possible to identify and trace deeply pigmented epithelial cells desquamated into the tubules which later found their way into the glomerular space (fig. 1). Pigmentation resulting from this cause cannot be regarded as glomerular in origin. The reticulum and lining cells of the capillary tuft and Bowman's membrane, as well as albuminous material occasionally seen in the capsular space, appeared bile stained in some cases. In rare instances it seemed that the cells lining Bowman's capsule either contained or were overlaid with a few granules of pigment.

Marked pigmentation of the renal epithelial cells began just proximal to the point where the tubule joins Bowman's capsule. The tubular epithelium of the cortex and, to a lesser degree, that of the medulla were stained yellow, green or brown. The location and intensity of the pigmentation varied somewhat in individual cases. The cells of the convoluted tubules, of the loops and of adjacent portions of the limbs of Henle appeared most deeply pigmented. The nuclei were often partly or completely obscured by collections of pigment granules about them. Pigment also seemed concentrated in or about occasional small vacuoles in the epithelial cells. Within the lumens of the tubules were bile-stained precipitated albumin, desquamated epithelial cells and dark brittle compressed casts. The latter structures were most numerous in the convoluted and straight collecting tubules and, in exceptional instances, appeared to occupy the lumens of the uriniferous tubules throughout their entire length.

Aside from marked pigmentation, the tubular epithelium in the majority of cases showed few regressive changes. In some instances the epithelial lining was somewhat swollen and encroached on the lumen of the tubule, but in others it appeared normal. Occasionally the epithelium was flattened and compressed by the bile casts. Few signs of necrosis were observed, and vacuolation and desquamation were slight or absent. The degree of parenchymatous degeneration was difficult to determine because of the pigmentation which obscured finer cytologic details. In exceptional instances regressive changes were marked in the tubular epithelium, irrespective of the degree of renal pigmentation or the duration of clinical jaundice. In these cases many epithelial cells in cross-section of one or several tubules were necrotic, disintegrated or desquamated, and hyaline casts were plentiful in the lumens.

OBSERVATIONS ON GROUP 2

In the thirteen cases of primary carcinoma of the head of the pancreas, in which death followed surgical decompression of obstructed biliary passages, there was a diminution in the degree of renal pigmentation, and regressive changes regularly became a prominent feature. The elimination of pigment from the tubular epithelial cells coincided with the appearance of small, irregular empty spaces and vacuoles in the cytoplasm which superficially resembled degenerative changes, the positive identification of which was difficult. In a few instances the picture in the kidneys appeared to be simply that resulting from a loss of pigment, the residuum of which, although irregularly distributed, seemed to remain longest in the lumens and epithelium of the collecting tubules and narrower portions of the limbs of Henle. The bile casts frequently crumbled before disappearing entirely, and in occasional cases the last vestiges of pigment consisted of a few bile casts

in the convoluted tubules. There appeared to be some delay in the loss of pigment from cells in which regressive changes were prominent, and even after most of the granular pigment had been eliminated the cytoplasm often remained diffusely stained.

Cortical regressive changes constituted the principal feature in these cases, being present over extensive areas embracing the cross-sections of several adjacent tubules and bearing no apparent relationship to the degree of pigmentation (fig. 2).

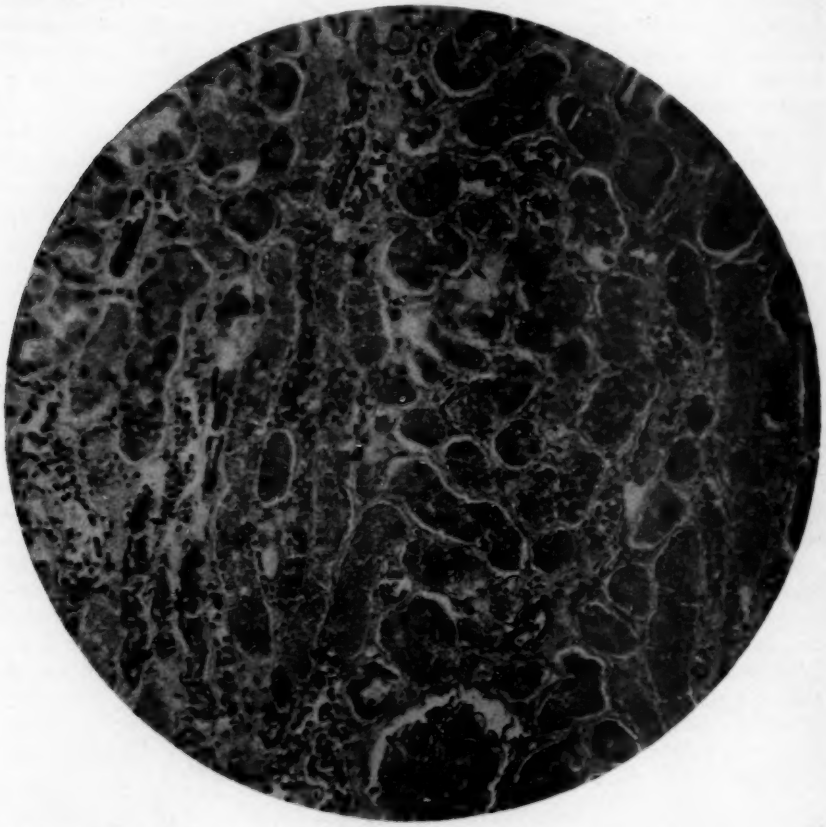

Fig. 2.—Photomicrograph (× 125), showing a nephrotic lesion associated with decompression of the common bile duct obstructed by pancreatic carcinoma. Note the regressive changes in the convoluted tubules and portions of the limbs of Henle.

Extensive necrosis, fine cytoplasmic vacuolation and complete cellular disintegration were common features. The lumens of these tubules occasionally contained precipitated albumin and hyaline casts in addition to desquamated epithelial cells. The regressive changes in the collecting tubules were similar in nature but usually less marked in degree, although hyaline casts were as a rule most numerous in them. The loss of cells through necrosis and desquamation was followed by regenerative processes characterized by mitosis, cellular hypertrophy, nuclear hyper-

chromasia, the presence of multinucleated giant cells and the development of a lining membrane consisting of an epithelial layer two or more cells deep. In certain instances two or more nuclei were apparently present in the same cell, but it was difficult to be certain whether this change had not resulted from obliteration of cell boundaries rather than from nuclear division.

The glomeruli in most instances appeared normal. Some, however, were shrunken, and in others the cells of the tuft were swollen and protruded into the lumen of the capillary loop. The epithelium lining Bowman's capsule was occasionally swollen, cuboid, vacuolated, necrotic and desquamated into the capsular space, which also contained precipitated albuminous material. The interstitial tissue was hyperemic, swollen and usually markedly edematous, especially in the medulla, where the collagen fibers were disarranged and widely separated. Such changes are present in diffuse glomerulonephritis, but the characteristic features of that condition were not observed in any case.

OBSERVATIONS ON GROUP 3

There was a variable degree of renal pigmentation in the seventeen cases of obstructive jaundice due to biliary calculi, in which death followed surgical decompression of the biliary system. The regressive changes were similar to those described for group 2 but were consistently much more marked in intensity and extent, with more actual cellular disintegration but a relatively less marked degree of pigmentation. Regeneration was similar in type but less marked than in the previous group.

OBSERVATIONS ON GROUP 4

The renal changes in the twelve cases of calculous cholecystitis without jaundice in which death followed surgical procedures about the biliary passages were characterized by absence of biliary pigmentation and by some degree of nephrosis in the majority of instances. In most cases the tubular damage was relatively less severe than in the two types of decompression (groups 2 and 3), and regeneration was an inconspicuous feature

COMMENT

It is apparent from the foregoing observations that aside from biliary pigmentation the parenchyma of the kidney usually presents relatively few regressive changes with complete and permanent obstruction of the common bile duct by pancreatic carcinoma. A widely accepted view is that bilirubin is a nontoxic substance. No impairment of the efficiency of the renal function from this cause is demonstrable in the majority of cases observed throughout the development and course of clinical obstructive jaundice. It is also probable that the bile acids have no deleterious influence on the kidney, at least in the later stages of obstructive jaundice, since the formation of these substances is usually suppressed and the quantity present in the blood, tissues and urine is much below that considered necessary for the production of toxic manifestations. The occasional occurrence of regressive renal changes in cases of this type, coupled with the appearance of acute insufficiency of hepatic function and renal failure, seems to indicate that these changes are dependent on other complicating factors, such as previous renal damage, infection, pancreatic necrosis, myocardial insufficiency and gastro-

intestinal disturbances. Chronic focal inflammatory lesions and senile arteriosclerotic changes in the renal vessels were frequently noted in the present study, and although these conditions are obviously not due to the effects of the obstructive jaundice per se, they probably contribute to the insufficiency of renal function, which occasionally develops under these circumstances. It was stated many years ago by Legg [17] that when bile pigmentation of the kidney and chronic nephritis co-exist they represent separate and distinct entities. Wilbur,[20] in a recent study of this aspect of the problem, found that the glomeruli are normal in the majority of cases of biliary nephrosis although there may be fine droplets of fat (Fahr [21]), precipitated albuminous material and slight swelling and even proliferation of the endothelial cells of some of the tufts. Most observers have failed to distinguish between the renal changes resulting from total biliary stasis and those associated with decompression induced by surgical procedures on the biliary passages or occurring spontaneously, as with release of an impacted calculus in the common bile duct.

In group 2 the outstanding features in the kidney following the re-establishment of bile flow from completely obstructed ducts consisted in cortical regressive changes present over extensive areas embracing the cross-sections of several adjacent tubules and bearing no evident relationship to the degree of pigmentation. The variability of these degenerative and necrotic lesions indicates that the factors responsible for their development are not invariably operative following decompression. The effects of the anesthesia under these circumstances are difficult to evaluate. No definite deductions could be made from observations on a single control case: A patient with obstructive jaundice due to carcinoma of the common hepatic duct was subjected to cholecystogastrostomy, which of course failed to relieve the biliary stasis. In this case, then, the factors of surgical procedure and anesthesia, but not that of decompression, were present. Death occurred eighteen hours after operation. Histologic examination of the kidney revealed the usual bile pigmentation and, in addition, a rather marked degree of degeneration and necrosis, still consistent, however, with what is encountered in exceptional cases of uncomplicated total biliary stasis. The fact that regressive renal changes were relatively more marked in the patients on whom surgical decompression had been performed (groups 2 and 3) than in nonjaundiced patients subjected to operative procedures on the biliary passages (group 4) suggests that the anesthetic and the operation were not the only factors responsible for the production of the renal damage.

21. Fahr, T., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, pt. 1, p. 282.

A comparison was made in individual cases between the lesions in the liver (Stewart and Lieber [22]) and those in the kidneys of patients dying after decompression of the biliary system obstructed by primary pancreatic carcinoma (group 2). In a number of instances the extent and degree of degeneration and necrosis in these two organs were closely parallel, especially in cases in which these changes were marked. In several others, however, no such parallelism could be demonstrated, and even in patients with acute diffuse necrosis of the liver regressive renal changes were sometimes mild or absent. Similarly, marked renal damage was occasionally present in patients in whom there were evidences of regeneration in the liver and very little, if any, hepatic damage. In the patients with calculous obstructive jaundice treated by decompression (group 3) the changes were more frequently equally severe in the liver and kidneys in individual cases. The significance of this observation is difficult to evaluate, but it may be dependent in part on the occurrence of repeated successive periods of acute calculous obstruction and spontaneous decompression with their consequent deleterious effects on the kidneys. In the patients of group 2 on whom surgical decompression had been performed there did not appear to be any definite relationship between the development of regressive renal changes and the time at which bile salts are known to appear in the bile following the release of obstruction of the common bile duct (Ravdin, Johnston, Riegel and Wright [23]). The theory that renal damage is due to the effect of toxic split protein products liberated from disintegrating hepatic tissue is not applicable to the cases in which there was a marked disproportion in severity between the regressive changes in the liver and those in the kidneys.

Studies of renal regeneration have been made in a number of instances of local and generalized lesions of the kidney occurring clinically or produced experimentally. In an extensive review of the literature on this subject no statements were found dealing with regenerative processes associated with nephrotic lesions in patients with total biliary stasis, or in those subjected to decompression or other operative procedures on the biliary passages. It may be assumed from our observations that regeneration accompanies recovery from this type as from other types of renal injury. The tubular epithelial cells which formed as a result of mitosis usually corresponded morphologically with the various individual types of cells found lining different portions of the uriniferous tubule normally. The material available was insufficient to determine the exact manner in which the necrotic tubular epithelium was disposed of, nor could the observations of certain investigators be confirmed, namely, that regenerating tubular epithelial cells grow in

22. Stewart, H. L., and Lieber, M. M.: Arch. Path. **18**:30, 1934.

23. Ravdin, I. S.; Johnston, C. G.; Riegel, C., and Wright, S. L.: J. Clin. Investigation **12**:659, 1933.

the form of a wedgelike sheet separating the necrotic elements from the membrana propria. There was no proliferation of connective tissue which could be ascribed to factors associated with biliary obstruction or decompression or with the multiplication of tubular epithelial cells. In the various types of cases included in the present study the evidences of renal regeneration were practically absent with total biliary stasis (group 1); they were less marked in group 4 than in the patients on whom decompression had been done (groups 2 and 3) and when present were usually a relatively inconspicuous feature.

The pathogenesis of these renal lesions is imperfectly understood. Some observers have suggested certain mechanisms whereby these changes might be produced. Of particular interest and significance is the demonstration by Helwig and Orr [24] of renal lesions practically identical in nature with those described as present in cases of traumatic pulpification and extensive hemorrhagic necrosis of the liver. Such observations suggest that this type of renal damage may be dependent on the elaboration of certain depressor substances (Ravdin [25] and Wilbur [20]) from the injured hepatic tissue or on the production of toxic split protein products by autolysis (Henschen [26]). It is believed that these substances reach the kidneys by way of the blood stream and by their elective affinity for parenchymatous elements (Volhard [27] and Helwig and Schutz [13]) or vascular structures (Helwig and Orr [24]) result in angiospasm (Furtwaengler [6]) and progressive degeneration and necrosis of the tubular epithelium.

Numerous observers have commented on certain obscure relationships between the liver and the kidneys. The literature dealing with this subject has been reviewed by Henschen [26] and Rosenbaum,[28] who with other recent investigators (Mayer,[29] Sacchetto and Oselladore,[30] Bompiani [31] and Koch [32]) have emphasized the intimate association of certain individual lesions occurring in these organs. According to Stäheli,[1] Dourmashkin [8] and Fitz-Hugh,[9] operative manipulation of the extraparenchymatous conducting system of either the liver or the kidney may result in reflex suppression of the functional activity of the other organ. Furthermore, clinical observations (Porges [33] and Grossmann [34]),

24. Helwig, F. C., and Orr, T. G.: Arch. Surg. **24**:136, 1932.
25. Ravdin, I. S.: Arch. Surg. **18**:219, 1929.
26. Henschen, C.: Deutsches Arch. f. klin. Med. **173**:488, 1932.
27. Volhard, F., in Mohr, L., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 1, p. 768.
28. Rosenbaum, J.: Deutsches Ztschr. f. Chir. **243**:66, 1934.
29. Mayer, E.: Virchows Arch. f. path. Anat. **236**:279, 1922.
30. Sacchetto, I., and Oselladore, G.: Arch. per le sc. med. **49**:310, 1927.
31. Bompiani, G.: Policlinico (sez. med.) **37**:266, 1930.
32. Koch, F.: Zentralbl. f. inn. Med. **53**:679, 1932.
33. Porges, O.: Wien. klin. Wchnschr. **40**:1640, 1927.
34. Grossmann, M.: Wien. klin. Wchnschr. **41**:450, 1928.

perfusion experiments (Asher and Meier,[35] Mosonyi and Voith[36]) and the results of administration of liver extracts to animals (Lampe,[37] Adlersberg and Gottsegen,[38] Kubo, Mitsui and Machita[39] and Glaubach and Mollitor[40]) suggest that the regulatory mechanism governing renal function may be influenced to some degree by a hormone elaborated in the liver and operating through humoral pathways. Additional evidence of similar import is supplied by the work of Gundermann,[41] Haberer,[42] Narath,[43] Mann,[44] Dicker and Anderson,[45] Allan, Bowie, McLeod and Robinson[46] and Whipple and Speed.[47]

The existence of a phylogenetic relationship has been demonstrated in fishes, amphibians, reptiles and other lower vertebrates and, according to Roger[48] and Spanner,[49] in birds, in which both the liver and the kidneys possess afferent portal veins. In mammals the kidneys have a portal venous supply in early embryonic life (Spanner), and although this tends to undergo involution there are indications that vestiges of it may persist and become functionally active in adults under certain conditions. Hemorrhages in the renal cortex, regressive changes in the epithelium of the renal tubules and the development of large, finger-like anastomoses between branches of the renal and portal veins have been encountered both in animals (Claude Bernard,[50] Villaret,[51] Tuffier

35. Asher, L., and Meier, H.: Biochem. Ztschr. **209**:200, 1929.

36. Mosonyi, J., and Voith, L.: Arch. f. exper. Path. u. Pharmakol. **173**:72, 1933.

37. Lampe, W.: Arch. f. exper. Path. u. Pharmakol. **119**:83, 1926.

38. Adlersberg, D., and Gottsegen, G.: Arch. f. exper. Path. u. Pharmakol. **142**:323, 1929.

39. Kubo, T.; Mitsui, T., and Machita, S.: Japan M. World **9**:43, 1929.

40. Glaubach, S., and Mollitor, H.: Wien. klin. Wchnschr. **42**:1437, 1929.

41. Gundermann, W.: Beitr. z. path. Anat. u. z. allg. Path. **90**:1, 1914.

42. Haberer, quoted by Furtwaengler.[6]

43. Narath, quoted by Furtwaengler.[6]

44. Mann, F. C.: Medicine **6**:419, 1927.

45. Dicker, E., and Anderson, C.: Compt. rend. Soc. de biol. **97**:1830, 1927.

46. Allan, F. N.; Bowie, D. J.; McLeod, J. J. R., and Robinson, W. L.: Brit. J. Exper. Path. **5**:75, 1924.

47. Whipple, G. H., and Speed, J. S.: J. Exper. Med. **21**:203, 1915.

48. Roger, G. H.: Traité de physiologie normale et pathologique, Paris, Masson et Cie, 1927, vol. 3, p. 30.

49. Spanner, R.: Verhandl. d. anat. Gesellsch. **33**:23, 1924; Ztschr. f. d. ges. Anat. (Abt. 1) **76**:64, 1925.

50. Bernard, C.: Les cous de physiologie appliquée à la médicine, Paris, J. B. Baillière, 1856, vol. 2, p. 313; Leçons sur les propriétés physiologiques et les alterations pathologiques des liquides de l'organisme, Paris, J. B. Baillière et Fils, 1859, vol. 2, p. 195.

51. Villaret, M.: Contribution à l'étude du syndrome d'hypertension portale. Les troubles du débit urinaire dans les affections hépatiques. Étude anatomique, expérimentale et clinique des territoires d'absorption et d'excrétion aqueuse, Tribune méd. **39**:133, 1907; Presse méd. **42**:1529, 1934.

and Léjars [52] and Villaret and Justin-Besançon [53]) and in human beings with increased portal pressure (Léjars, Giacomini, Henle, Virchow and Hyrtl [54]). According to Rosenbaum,[28] this vascular mechanism may be responsible in part for the occurrence of renal changes following extensive damage to the liver, some of the blood from the portal vein being carried directly to the kidney by way of the ordinarily unused collateral blood channels.

Despite these various hypotheses of anatomic, functional and phylogenetic relationships between the liver and the kidneys, the pathogenesis of the renal changes associated with extensive hepatic damage and operative procedures on the biliary passages remains problematic. On the basis of the observations made in the present study no sharp differentiation can be made between the renal lesions noted after decompression of the obstructed biliary system and those following operation on the nonobstructed biliary tract. Although the former appeared to be generally more marked, the extreme variability of human pathologic material and the difficulty of evaluating the influence of several variable and uncontrollable factors operative in such cases render it impossible to attribute much importance to such quantitative differences.

SUMMARY

The renal changes associated with biliary obstruction and decompression and with surgical procedures on the biliary tract in nonjaundiced patients with calculous cholecystitis are described and discussed.

Regressive cellular changes in the kidney were relatively slight in extent and intensity in cases of uncomplicated total stasis; they increased markedly with decompression and were present in many nonjaundiced patients subjected to surgical procedures on the biliary tract.

No sharp differentiation could be made between the renal lesions following decompression and those following operation on the nonobstructed biliary tract, although the former were generally more marked in extent and intensity.

The extent of regressive changes in the kidneys frequently paralleled that of those in the liver in individual patients with biliary decompression.

52. Tuffier and Léjars, quoted by Villaret, M., and Justin-Besançon, L.[53]

53. Villaret, M., and Justin-Besançon, L.: Nouveau traité de médicine, Paris, Masson et Cie, 1928, vol. 16, p. 133.

54. Léjars; Giacomini; Henle, Virchow and Hyrtl, quoted by Henschen, C.: Arch. f. klin. Chir. **173**:488, 1932.

HISTOLOGIC STUDIES ON THE SPLEEN IN CASES OF LEUKEMIA

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In the routine microscopic examination of spleens removed at autopsy in cases of leukemia I have often observed changes in the trabeculae which, according to my knowledge, have so far been given little attention and which are likely to throw light on the histogenesis of leukemic lesions. These changes consist of the gradual transformation of the trabeculae into leukemic tissue. This transformation is sometimes so marked that the small trabeculae can be traced only in serial sections and by the use of the special staining methods for connective tissue fibers. In rare instances the trabeculae are actually decreased in number; this is particularly striking in cases in which the spleen is only slightly enlarged. Lubarsch [1] mentioned that in cases of myelosis even large sections may fail to show a single trabecula. The transformation of the trabeculae does not depend on the type of leukemia, the age of the patient or the duration of the disease. It is found in acute cases as well as in chronic ones.

MATERIAL AND METHODS

The study is based on fifty-one cases of leukemia. The following types are represented: stem cell leukemia (hemocytoblastosis), eleven cases; lymphadenosis, ten cases; myelosis, twenty-four cases; monocytic leukemia, four cases, and giant cell leukemia (megakaryocytosis), two cases. The cases are summarized in the table, which also gives the extent of the leukemic changes in the trabeculae.

The material was fixed in Zenker's solution after the method of Helly and Maximow and in a dilute solution of formaldehyde U. S. P. (1:10). The material fixed in Zenker's solution was stained after the methods of Giemsa, Van Gieson, Weigert (for elastin), Heidenhain (azocarmine) and Foot (silver impregnation). The sections fixed in formaldehyde were used for the hemalum-eosin stain, the stains for fat (sudan III, nile blue sulphate) and the tests for iron (prussian blue) and oxidase (Goodpasture).

From the Department of Pathology of the Cook County Hospital and the Uihlein Memorial Laboratory of the Grant Hospital.

1. Lubarsch, O.: Pathologische Anatomie der Milz, in Henke, F., and Lubarsch, O.: Handbuch der speziellen Pathologie und Histologie, Berlin, Julius Springer, 1927, pt. 2, vol. 1.

Summary of Data in Cases Studied

Case	Age, Years	Sex	Race	Type of Leukemia	Duration of Illness	Weight of Spleen, Gm.	Leukemic Changes: About the Intratrabecular Blood Vessels	Leukemic Changes: In Small Trabeculae
1	4	M	Negro	Stem cell leukemia.....	6 days	110	0	±
2	3	F	White	Stem cell leukemia.....	1½ wks.	200	++	++
3	27	F	Negro	Stem cell leukemia.....	1 mo.	500	++	+
4	4	M	White	Stem cell leukemia.....	6½ wks.	100	±	+
5	22	F	Negro	Stem cell leukemia.....	7 wks.	555	++	++
6	35	M	White	Stem cell leukemia.....	8 wks.	205	±	±
7	23	M	White	Stem cell leukemia.....	12 wks.	495	++	±
8	6	M	White	Stem cell leukemia.....	3 mos.	155	++	++
9	30	M	White	Stem cell leukemia.....	4 mos.	1,015	++	+
10	11	M	Negro	Stem cell leukemia.....	8 mos.	120	+	+
11	20	M	White	Stem cell leukemia (aleukemic)	11 mos.	950	+	++
12	8	M	White	Acute lymphadenosis	4 wks.	100	++	+
13	34	M	White	Acute lymphadenosis	3 mos.	600	+	+
14	19	M	Filipino	Acute lymphadenosis (subacute course; acute exacerbation; roentgen treatment)	4 mos.	170	++	+
15	48	M	White	Chronic lymphadenosis (death following an acute exacerbation)	4 mos.	2,865	+	++
16	57	M	White	Chronic lymphadenosis	9 mos.	1,810	0	0
17	64	M	Negro	Chronic lymphadenosis	9 mos.	240	±	+
18	47	M	White	Chronic lymphadenosis (aleukemic; acute leukemic exacerbation; roentgen treatment)	11 mos.	1,400	+	++
19	62	M	White	Chronic lymphadenosis (roentgen treatment; death from septicemia)	1 yr., 4 mos.	2,665	++	±
20	54	M	White	Chronic lymphadenosis (acute exacerbation; roentgen treatment)	2½ yrs.	250	++	±
21	66	M	White	Chronic lymphadenosis (death from carcinoma of prostate)	Several years	1,130	±	±
22	74	M	White	Acute myelosis (complicated by melanoma of the eye)	4 wks.	350	+	+
23	33	M	White	Acute myelosis	5 wks.	318	+	±
24	13	M	White	Acute myelosis	6 wks.	590	+	+
25	38	F	White	Acute myelosis (aleukemic)	7 wks.	410	+	++
26	51	M	White	Subacute myelosis	3½ mos.	240	++	+
27	26	M	White	Subacute myelosis	3½ mos.	2,480	+	+
28	50	M	White	Subacute myelosis (aleukemic)	4 mos.	650	+	+
29	66	M	White	Subacute myelosis	4½ mos.	460	+	+
30	78	M	White	Subacute myelosis	4½ mos.	435	±	0
31	59	F	White	Subacute myelosis	6 mos.	1,540	0	++
32	36	M	White	Chronic myelosis (roentgen treatment; death from red encephalomalacia)	8 mos.	2,120	++	++
33	26	M	White	Chronic myelosis	8 mos.	3,840	++	++
34	53	M	Negro	Chronic myelosis (acute exacerbation without treatment 3 wks. prior to death)	1 yr.	440	+	+
35	60	F	Negro	Chronic myelosis (roentgen treatment; death from acute endocarditis)	1 yr.	535	+	±
36	46	M	White	Chronic myelosis (complicated by pulmonary tuberculosis)	1½ yrs.	400	0	±
37	39	M	White	Chronic myelosis (death from erysipelas)	1½ yrs.	1,215	+	+
38	38	M	White	Chronic myelosis (acute exacerbation; roentgen treatment)	1¾ yrs.	1,660	0	±
39	34	F	White	Chronic myelosis (acute exacerbation; roentgen treatment)	2 yrs.	2,095	+	+
40	52	M	White	Chronic myelosis (acute exacerbation without treatment)	3½ yrs.	930	+	+
41	58	F	White	Chronic myelosis (subleukemic)	5 yrs.	860	0	±
42	48	M	White	Chronic myelosis (roentgen treatment; death from pericarditis)	5¾ yrs.	1,050	+	+

Summary of Data in Cases Studied—Continued

Case	Age, Years	Sex	Race	Type of Leukemia	Duration of Illness	Weight of Spleen, Gm.	Leukemic Changes: About the Intratrabecular Blood Vessels	Leukemic Changes: In Small Trabeculae
43	60	F	White	Chronic myelosis (death from portal thrombosis)	8 yrs.	1,950	0	0
44	64	M	White	Chronic myelosis (death from cerebral hemorrhage)	Undetermined	775	+	++
45	31	F	White	Chronic myelosis (acute exacerbation; roentgen treatment)	Several years	280	0	±
46	46	F	Negro	Monocytic leukemia	2½ wks.	250	+	+
47	36	M	White	Monocytic leukemia	2½ wks.	550	++	++
48	54	M	White	Monocytic leukemia	2 mos.	500	++	++
49	28	M	Chinese	Monocytic leukemia	10 wks.	190	±	±
50	14	M	White	Giant cell leukemia (aleukemic)	10 wks.	580	0	+
51	59	M	Negro	Giant cell leukemia.....	Undetermined	585	+	+

COMMENT

In the larger trabeculae, which carry blood vessels, the leukemic transformation starts underneath the endothelium of the veins. This subendothelial leukemic infiltration has been described in the literature, and Lubarsch referred to it in his discussion of the splenic changes in cases of lymphatic leukemia. He stated that the subendothelial lymphatic tissue may appear as a uniform layer or may bulge into the lumen in the form of circumscribed nodules. Fried [2] mentioned a heavy invasion by lymphoid cells of the splenic veins in a case of leukemic lymphadenosis. Semsroth [3] described a marked subendothelial accumulation of pleomorphic cells in the splenic veins in a case of primitive cell leukemia. Lubarsch pointed out that these proliferations take their origin from a cellular layer which seems to be easily stimulated. (I have often found subendothelial cell proliferation of the trabecular veins of the spleen in cases of infectious diseases, especially in cases of acute septicemia, malignant endocarditis, sepsis lenta, tularemia and typhoid. In these conditions the proliferations consist of histiocytes, lymphocytes and plasma cells. In cases of scarlet fever with generalized lymphoblast and plasma cell reaction the changes in the splenic veins may be as marked as in cases of leukemia, and thick layers of large lymphoid cells and plasma cells are found underneath the endothelium of the veins. The leukemic infiltrations are composed of the cells which are characteristic of the type of leukemia present. There are, however, sometimes slight differences between the cellular picture of the pulp and the predominating type of cell in the subendothelial formations. In cases of chronic myelosis, for instance, promyelocytes may outnumber the cells of other types in the pulp, while the subendothelial layers consist chiefly of myeloblasts. In cases of stem cell leukemia the subendothelial layers

2. Fried, B. M.: Arch. Path. **2**:23, 1926.
3. Semsroth, K.: Folia haemat. **52**:144, 1934.

may show a tendency to differentiate into atypical cells of the erythropoietic series. In addition to the leukemic cells, one often finds single lymphocytes, plasma cells and histiocytes which may be filled with iron pigment. These cells are encased in a delicate net of fine fibrils which extends from the endothelium to the compact portion of the trabeculae. The endothelial cells are stretched and flattened but resist the piling up of the cells, and even large nodules which bulge far into the lumen of the vein are still covered by an intact endothelium (fig. 1).

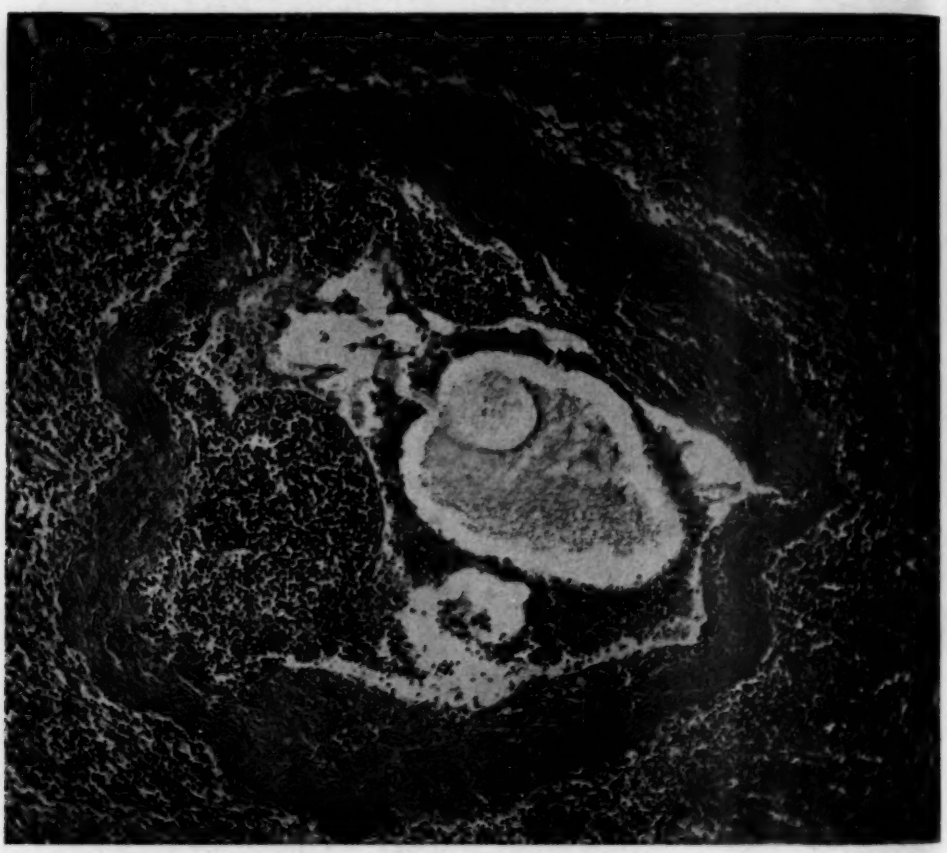

Fig. 1.—Subendothelial nodules of lymphatic tissue in an intratrabecular vein of the spleen in a case of chronic lymphadenosis. Giemsa's stain; × 150.

The trabecular veins do not have a differentiated wall. The endothelium rests directly on the dense connective tissue of which the trabeculae are composed (Weidenreich,[4] Sobotta[5] and Hartmann[6]).

4. Weidenreich, F.: Arch. f. mikr. Anat. **58**:247, 1901.

5. Sobotta, J.: Anatomie der Milz, Jena, Gustav Fischer, 1914.

6. Hartmann, A.: Die Milz, in von Moellendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, pt. 1, vol. 6.

Hartmann found the tissue underneath the endothelium to be slightly more cellular than that in the remaining parts of the trabeculae. Where the trabecular veins enter the pulp, rows of leukemic cells may be seen extending from the pulp into the trabecula along and underneath the endothelium. The heavy cellular mantles about the large veins, however, are often completely separated from these areas of local invasion, and since there is no evidence of an emigration of the leukemic cells from the lumens of the veins and similar changes also occur in aleukemic conditions, the cell mantles apparently take their origin from an activation and proliferation of the subendothelial mesenchyme. Progressing

Fig. 2.—Diffuse leukemic infiltration of a trabecula in a case of acute monocytic leukemia. The outlines of the trabecula are still visible. In the center is a vein lined by intact endothelium. Van Gieson's stain; × 150.

gradually toward the periphery, more and more of the dense connective tissue about the veins becomes transformed into a loose net the meshes of which are filled by leukemic cells. Finally, only a few connective tissue fibers stained red with Van Gieson's stain and elastin fibers are left marking the outlines of the trabecula. In the center the endothelium-lined lumen of the vein persists (fig. 2).

In this connection it may be mentioned that the subendothelial formation of leukemic tissue is not restricted to the splenic veins but occurs

also in the veins of other organs, for instance, the liver and the lung. In these organs, too, the nests of cells originate locally from the subendothelial mesenchyme, as is evidenced by the fact that the leukemic changes of the veins can be found also in areas in which no extravascular infiltrations are present.

Forkner [7] described a lifting of the endothelium of the larger arteries from the media by a considerable accumulation of monocytes in the spleen in a case of monocytic leukemia. In my material subendothelial formation of leukemic tissue has not been present in the arteries. Entering the trabeculae, the arteries retain their independence. Their adventitial layer is well developed and loose (Hartmann). It is this loose adventitial tissue which may become the site of leukemic changes, and the arteries are then found surrounded by a broad layer of leukemic cells. These changes are, however, less common than the subendothelial infiltrations of the veins.

The leukemic infiltrations are not restricted to the larger trabeculae, which contain veins and arteries. The smaller and smallest trabeculae often show similar changes, and, especially in the small trabeculae, the leukemic infiltration is sometimes extremely striking. The infiltration starts in the periphery or in the center of the trabeculae. In the former instance the contours of the trabeculae become irregular lamellae of collagenous bundles, being chipped off by rows of cells which accumulate between them. This chipping off of connective tissue bundles is not to be confused with the strands of collagenous fibers which normally radiate from the trabeculae into the reticulum of the pulp. These strands are free from elastin fibers, while in the case of leukemic separation the bundles are rich in elastin tissue. With increasing accumulation of cells the connective tissue bundles become more and more separated and frayed out (fig. 3) until they disappear completely together with the elastin fibers. The trabecula has been transformed into a fine reticulum which can hardly be distinguished from the reticulum of the adjacent pulp. In the center of the trabecula the process starts with the appearance of single leukemic cells between the connective tissue bundles. These cells push the collagenous and elastin fibers apart, and when the cells multiply to form small nests a fine reticulum appears between them. One can speak of a desmolytic transformation of the collagenous tissue into a blood cell-forming reticulum. This transformation of dense connective tissue into leukemic tissue reminds one of the leukemic changes of the valves of the heart described by Siegmund.[8] Occasionally the intratrabecular cell nests are found near fine capillary blood vessels. In cases of generalized infections with marked activation of the mesenchyme I have sometimes seen small groups of histiocytic cells near these fine intratrabecular capillaries.

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7. Forkner, C. E.: Arch. Int. Med. **53**:1, 1934.
8. Siegmund, H.: Virchows Arch. f. path. Anat. **290**:1, 1933.

Where do the intratrabecular leukemic cells originate? The simplest explanation is that the cells originate in the pulp and migrate into the trabeculae. In serial sections the intratrabecular cell nests, however, often lack connection with the pulp. The cells in the trabeculae may differ from the cells in the surrounding pulp. They may be more mature or less differentiated. Certain changes suggest a local origin of the cells from preexistent elements. The trabeculae of the spleen con-

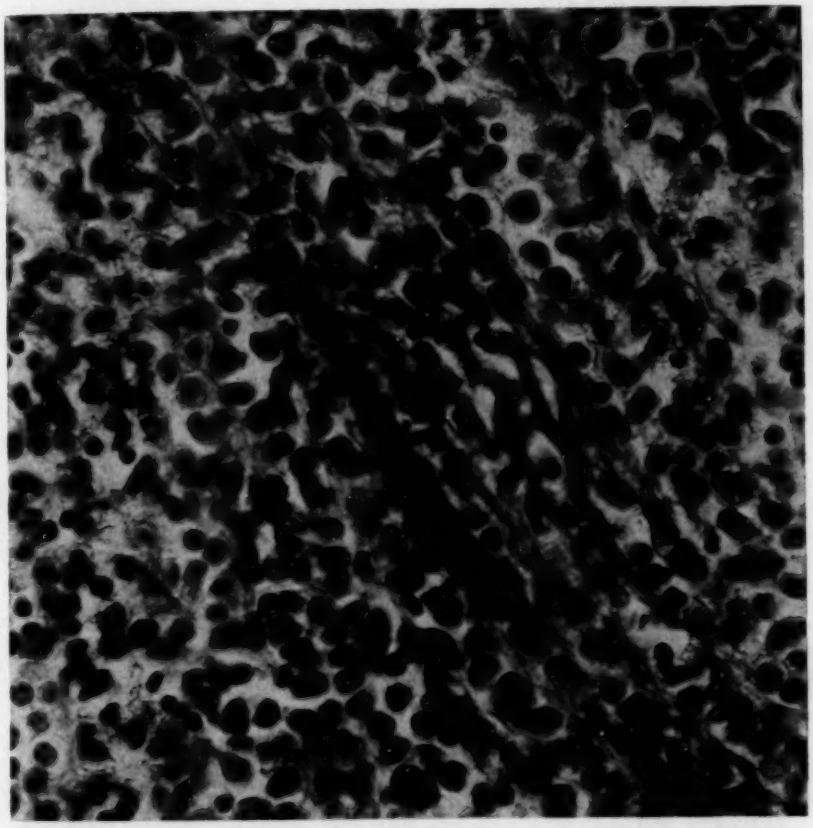

Fig. 3.—Small trabecula broken up into several connective tissue bundles by rows of leukemic cells (same condition as shown in figure 2); × 150.

sist of a dense connective tissue richly interwoven with elastin fibers and enclosing a few smooth muscle fibers. Wedged in between the connective tissue fibers there are single long and flat nuclei about which no cytoplasmic body is discernible. In cases of splenic siderosis iron granules may accumulate about these nuclei. In case of intratrabecular blood cell formation the first change to become visible is a swelling of the nuclei. The nuclei assume a round or oval shape, and the chromatin

granules form a fine net. The swollen nuclei are surrounded by a distinct rim of homogeneous cytoplasm, and if the type cell of the particular case of leukemia shows a positive oxidase reaction, oxidase granules are already present in this early stage of differentiation. The granules bring out most clearly the long, flat and branched shape of the cell. Later, the cell loses the connection with the ground substance and becomes rounded. A clear space separates the cell from the surrounding fibrils

Fig. 4.—Center of a small trabecula in a case of acute monocytic leukemia. In addition to a few flat nuclei of fibrocytes, one sees larger nuclei which show a distinct chromatin structure. Some of these nuclei are still closely surrounded by connective tissue bundles, while others have become separated by a fine, clear space and reveal a distinct cell body. Note the deeply stained oxidase granulation in some of the cells. Oxidase reaction; × 1,000.

(fig. 4). The nucleus divides by mitosis, and the fibrocyte has changed into a leukemic cell which may be a hemocytoblast, lymphatic cell, monoblast, myeloblast or young myelocyte according to the type of leukemia

present. The activated fibrocyte may directly pass into the differentiated progenitors of blood cells without going through the hemocytoblast stage.

In a preceding paper [9] I said that in cases of leukemia the fibroblasts of young granulation tissue may become transformed into immature blood cells. The leukemic changes in the splenic trabeculae indicate that also the resting fibrocyte may display blood cell-forming potencies and that the leukemic process is characterized by the hemocytopoietic activity of the entire mesenchyme. In this process of blood cell formation the capsule of the spleen (and also of the liver and the lymph nodes) may take part. According to Hartmann, the capsule of the spleen consists of three layers, namely, two outer layers of dense connective tissue and an inner layer, which is less compact and more cellular. It is this inner layer which may become transformed into leukemic tissue. In cases of acute leukemia this transformation may also spread to the outer layers, and a thin layer of connective tissue only may be left on which the mesothelium rests. In a case of acute erythroblastosis, Pinkerton [10] described the capsule and the trabeculae of the spleen so densely infiltrated by nucleated red cells that these structures were difficult to distinguish from the pulp.

SUMMARY

In cases of leukemia the trabeculae and the inner layer of the capsule are often involved by the leukemic process. In the larger trabeculae the leukemic tissue develops underneath the endothelium of the veins and, less frequently, in the adventitia of the arteries. In the smaller trabeculae the peripheral portions are gradually incorporated into the pulp, and nests of leukemic cells appear also in the center of the trabeculae. The cells in the center seem to originate locally from the fibrocytes.

The changes have been observed in cases of acute stem cell leukemia, acute, subacute and chronic myelosis, acute and chronic lymphadenosis, monocytic leukemia and giant cell leukemia.

9. Jaffé, R. H.: Arch. Path. **14**:177, 1932; **18**:763, 1934.
10. Pinkerton, H.: Arch. Path. **7**:567, 1929.

VITAL STAINING OF MICROGLIA

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The reaction of nerve tissue toward colloidal vital dyes, such as trypan blue, has given great support to the concept of a protective barrier between the blood stream and the brain, unique for the nervous system. Other tissues of the body stain freely; the brain does not. For many authors this fact is explained by the so-called hemato-encephalic barrier. That the vascular supply of the brain possesses properties of an entirely different order from those of the other organs is a concept of extreme theoretical and practical importance. But the evidence for this hypothesis, so far as it is drawn from vital staining, is open to another explanation, namely, that the virtual absence of vital staining in the brain is due, not to a vascular barrier, but to an intrinsic lack of affinity for the dye.

For the study of this problem the vital staining of microglia offers a fruitful approach. Although under suitable conditions these cells may have certain properties of phagocytosis and ameboid movements in common with macrophages of other parts of the body, there is a profound difference in the reaction to trypan blue. DeAsua,[1] who considered the microglia as part of the reticulo-endothelial system, expressed a belief that the normal absence of vital staining, perhaps the chief difference between microglia and macrophages, is due to a vascular barrier which withholds the dye. The fact that with repeated large doses administered to an otherwise normal animal the microglia may stain slightly perhaps lends support to the theory.

On the other hand, it is well known that when microglia are active, i. e., undergoing morphologic changes that accompany phagocytic activity, they may store trypan blue. The most frequently used experimental method of producing this condition is trauma, resulting in inflammation and destruction of tissue. However, in addition to activating the microglia, such a process of inflammation invariably raises the permeability of the blood vessels. The altered permeability of the vessels under these conditions has been one of the main arguments in favor of the concept of a hemato-encephalic barrier.

A different approach to the problem of the nature of the reaction of nerve tissue toward colloidal dyes would be to activate the microglia

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1. de Asua, F. J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:354, 1927.

without simultaneously raising the permeability of the blood vessels. Such a method is offered by the study of secondary degeneration of fiber tracts at a distance from a lesion. The reaction of such degenerating areas is entirely gliogenous in the early and middle stages, with the microglia playing an important rôle. The classic description of the process of secondary degeneration was given by Jakob,[2] who worked with the older staining methods. Recently Cramer and Alpers [3] have repeated the work with the use of the newer impregnation technics.

PROCEDURE

Observations were made on a series of nine rabbits. With aseptic precautions and with the animal under anesthesia induced by pentobarbital sodium, ether or a combination of the two, the spinal cord was exposed in the middle or upper part of the lumbar region. In the earlier experiments a complete hemisection was performed; later an attempt was made to involve only the posterior columns. In some instances the scalpel was heated before the incision was made. The animals were allowed to survive for from eight to fourteen days. During this period from six to ten injections of trypan blue were given. The most satisfactory method of administration was found to be a subcutaneous injection of 5 cc. of a 2 per cent solution. The total amount of dye administered to an animal ranged from 0.6 to 1 Gm. of the dry powder.

The spinal cord of each animal was removed immediately after death. All the cords were free from infection, as evidenced by gross and subsequent microscopic observation. From different levels of the cord blocks were fixed in Heidenhain's Susa mixture [3a] for cell study and observation of trypan blue, formaldehyde solution of ammonium bromide for silver stains and potassium bichromate for the Marchi method. In all instances the block containing the lesion was fixed in Susa's mixture.

Material fixed in Susa's mixture was transferred after two hours directly to 95 per cent alcohol, where it was kept with several changes for from three to four hours. After being treated with absolute alcohol and a mixture of absolute alcohol and chloroform for another three hours, the blocks were cleared in chloroform and embedded in paraffin. Sections were cut 8 microns thick and stained with Meyer's paracarmine. The speed in dehydration and the use of an alcoholic stain were deemed essential for the retention of all the dye in the tissues. The paracarmine, after the fixation in Susa's mixture gave an excellent picture for nuclei and Nissl bodies. In addition, appropriate stains for collagen and reticulum were used when indicated. For Marchi stains the classic method was used. The silver carbonate for the impregnation of the microglia was prepared by the method of Kubie and Davidson.[4]

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2. Jakob, A.: Ueber die feinere Histologie der sekundären Faserdegeneration in der weissen Substanz des Rückenmarks, in Nissl, Franz, and Alzheimer, Alois: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1913, vol. 5, p. 1.

3. Cramer, F., and Alpers, B. S.: Arch. Path. **13**:23, 1932.

3a. Susa mixture consists of mercuric chloride, 4.5 Gm.; sodium chloride, 0.5 Gm.; trichloracetic acid, 2 Gm.; acetic acid, 4 cc.; solution of formaldehyde, 20 cc., and water, 80 cc.

4. Kubie, L. S., and Davidson, D.: Arch. Neurol. & Psychiat. **19**:888, 1928.

OBSERVATIONS

On gross observation the white matter at the site of the lesion was stained light blue. When the cord was cut up into small blocks for fixation, the subjacent gray matter was also seen to be stained. This macroscopic color extended upward from the lesion for a variable distance, as much as 2 cm. in extreme cases, although, of course, the intensity was much diminished. The macroscopic color gradually faded, and the remainder of the cord was completely uncolored. The dura, however, was tinted light blue throughout its whole extent, the color being most intense at the angles formed by the nerve roots.

The histologic description may be divided into three parts. Opposite extremes were presented by the lumbar portion of the cord at the site of the lesion and the cervical portion of the cord. The intermediate regions showed a transition between these extremes.

Lesion.—At the site of the lesion all possible cell elements stained vitally—neurons, the ependyma, all types of glia, macrophages in the vascular adventitia, gitter cells of diverse origin, capillary endothelium and fibroblasts which had grown in.

Morphologic changes in the neurons were often severe. At the site of the lesion the number of ganglion cells was sharply diminished. The surviving cells showed varying changes, from shrinking and pyknosis to marked swelling and chromatolysis, with gradations between these extremes. There was a mild increase of glial nuclei around the surviving neurons. A few millimeters from the lesion these neuronal changes were not nearly so pronounced.

The cord of one animal in the series was somewhat anomalous. In this almost every ganglion cell at the site of the lesion was diffusely stained with trypan blue. The nuclei were usually involved. The cells were shrunken, with dark clumps of Nissl substance clearly visible. Frequently the nucleus, stained dark blue, was partly projecting from the perikaryon, as if in the process of extrusion. This cord contrasted with others in the intense staining of the neurons and the slight amount of trypan blue in other cellular elements. All the other cords showed extremely little dye in the neurons and large amounts in other cells.

Except in this one cord vitally stained neurons were encountered rarely. Both granular and diffuse storage were observed. In the series as a whole, however, the slight amount of vital staining of the neurons, in spite of the severe morphologic changes, was striking, especially in comparison with the large amounts of trypan blue seen elsewhere in the sections.

In three cords ependymal cells were vitally stained. They were swollen and slightly vacuolated, containing a few fine granules of trypan blue. Such cells were sometimes found desquamated in the

central canal. Invariably where vitally stained ependymal cells were found, other sections from the same block about 0.5 mm. distant showed no granules, in spite of similar morphologic changes.

Glial alterations in the gray matter were not pronounced when examined in carmine preparations. There was a great increase in the total number of nuclei, but little cytoplasm was visible. Near many of the nuclei a few middle-sized granules of dye could be found. Figure 1 illustrates the type of dye storage in the gray matter, showing a few

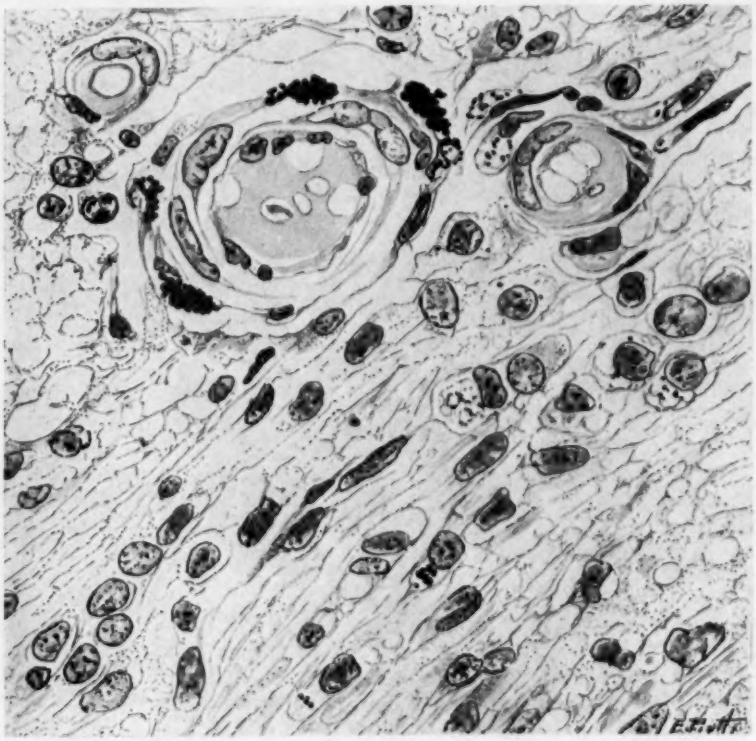

Fig. 1.——Gray matter, from the posterior horn, close to the lesion. Vitally stained macrophages are seen in the perivascular sheaths, with a few vitally stained glia cells. The glia cell in the center at the right in the lower part of the picture is much more heavily stained than is usual. Camera lucida drawing; × 760.

vitally stained glia cells near some heavily stained macrophages. These glia cells were chiefly microglia, but some could be positively identified as oligodendroglia.

Figure 2 is a photomicrograph of a silver carbonate preparation, taken from the block adjacent to the lesion, showing active microglia in the gray matter eleven days after the injury. A particularly heavy vital staining of these cells was shown in carmine-stained sections from this

specimen. The morphologic changes in the microglia were pronounced but appeared only in silver preparations.

In the white matter, on the other hand, glial changes were apparent with the simple carmine stain. Different stages in the transformation of microglia into gitter cells could be followed; at first a slight amount of cytoplasm was visible, with gradations to large amounts having many pseudopods and processes and gradually enclosing more and more lipoid globules. In the cytoplasm of such cells there were often a few granules of trypan blue, requiring high magnification for identification. On the whole, however, the amount of dye in the glia of the white matter was not great, either in the gitter cells or in the transitional forms of microglia.

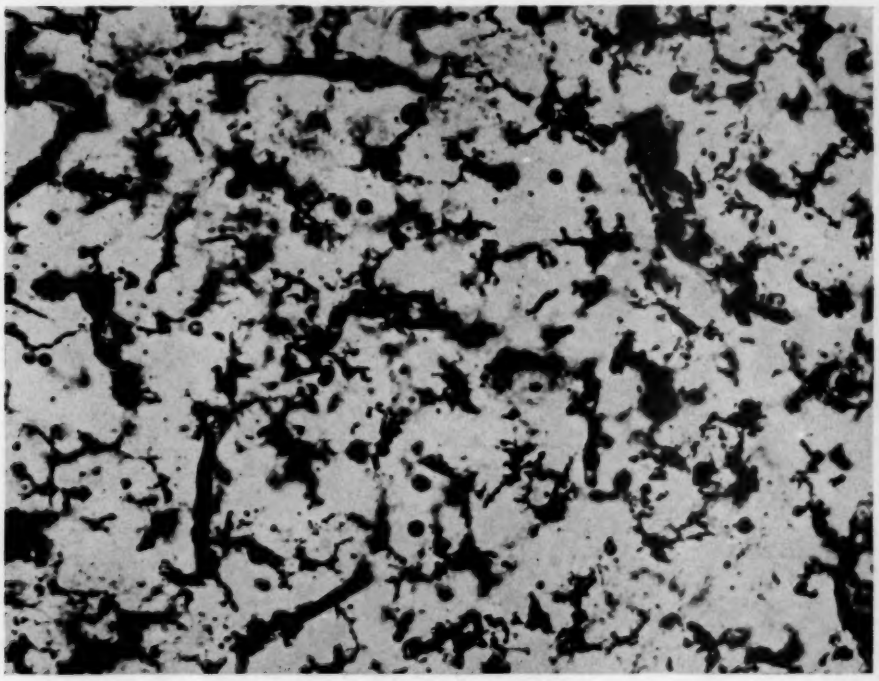

Fig. 2.—Microglia in the gray matter, a few millimeters above the lesion. Corresponding sections stained with paracarmine show numerous granules of trypan blue. Silver carbonate; × 700.

Occasional granules of trypan blue were also found in swollen astrocytes, in which the cytoplasm had a glassy, homogeneous appearance but the nuclear form attested to the integrity of the cells.

The dye was found abundantly in the capillary endothelium and in the adventitia of the larger blood vessels. Under low magnification the blood vessels stood out sharply, with large blue dots at their

margins. Under higher magnification these blue dots were resolved into macrophages containing numerous large granules. Figure 1 shows well the type of storage in the adventitia of a blood vessel and the way this contrasts with the storage in glia cells of the immediate neighborhood. The capillary endothelial cells contained considerable amounts of trypan blue in the form of a few small to middle-sized granules at one or both poles of the enlongated nuclei.

It is noteworthy that vital staining in relation to the blood vessels was found all over the section and was not necessarily concentrated in the focus of most intense cellular activity. Such blood vessels were found, for example, in the ventral white matter, where the glial reaction was absent. In addition, a short distance above the actual lesion, where the cells of the anterior horn were but slightly affected by the injury, the blood vessels showed considerable trypan blue.

Indeed, the sharpest contrast between the vital staining of glia and that of macrophages and endothelium was to be found not in the focus of injury but a few millimeters above it. In comparison with the lesion, the glia cells contained much less trypan blue, while the adventitial cells contained only a little less.

At the site of the lesion the reparative process entailed a greatly increased vascularity. The large number of new blood vessels, with vitally stained macrophages in their adventitia, helped to accentuate the difference between the glial and the perivascular storage. In spite of the increase of the blood vessels in the white matter, the gray matter had the richer vascularity. Dye-laden adventitial macrophages were more numerous in the gray than in the white matter, even at the site of the lesion.

The reparative process also brought about an ingrowth and proliferation of connective tissue and macrophages derived from the dura. In the majority of the cords, though not in all, fibroblasts were clearly visible in some part of the lesion. Strands of collagen and reticulum invaded the nerve tissue to a variable depth, well brought out by appropriate collagen stains but easily discernible in the carmine preparations. Such fibroblasts frequently contained granules of trypan blue. The macrophages invading from the dura were often intensely stained with the dye.

The transition from microglia to gitter cells, briefly mentioned heretofore, has been frequently described in the literature. The transformation of nonglial elements, such as macrophages, into gitter cells has not received so much attention. In certain instances this transformation could be extremely well followed, as figure 3 illustrates. At the onset of the reaction the macrophage is heavily laden with granules of trypan blue but shows no fat vacuoles. Gradually more and more of the lipoid material is ingested, causing the cell to become larger and more vacuolated. Simultaneously the granules of dye become more dispersed

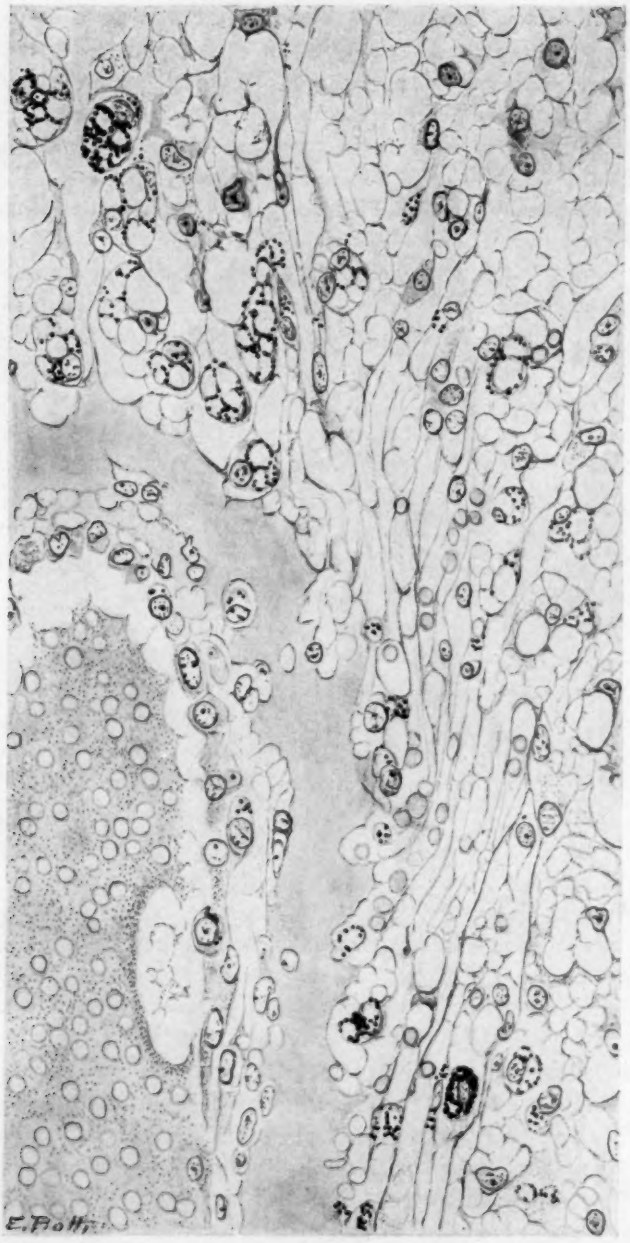

Fig. 3.—Blood vessel at the site of the lesion, showing transformation of vitally stained perivascular macrophages into gitter cells. Note the vital staining of the endothelium. Camera lucida drawing; × 400.

in the attenuated cytoplasm, and the individual granules appear smaller and more numerous than in the cell without lipoid inclusions. So far as the fat content is concerned, the gitter cell derived from the macrophage is quite indistinguishable from the cell derived from the microglia. But the trypan blue content in the former is vastly greater than that of the latter. This is obviously correlated with the greater amount of dye in the macrophages before lipoid phagocytosis has commenced. Figure 4*A* is a photomicrograph of the blood vessel shown in figure 3, about 0.5 mm. distant. The full extent of the gitter cell formation is shown. Transitional stages are not so apparent. The abundant storage of trypan blue does not reproduce in the photograph.

Transformation of capillary endothelium into wandering cells was also observed, although rarely. Figure 4*B* is a photomicrograph of such a process. The endothelium can be seen passing through the various stages from mild swelling of the cytoplasm to a complete rounding up. The nucleus becomes round instead of remaining elongated. The cytoplasm seems to be completely detached from the capillary wall, and finally similar cells may be seen outside the blood vessel wall. These cells contain only a relatively few rather fine granules of trypan blue, which unfortunately are not visible in the photomicrograph. The dye content of such derived wandering cells is much less than that of the dural macrophages. This process of change in the endothelial cells was rare.

Cervical Region.—An altogether different picture was presented by the cervical segments. Even in the carmine preparations the areas of secondary degeneration in the posterior columns (and, where involved, the dorsal spinocerebellar tracts) were easily discernible. In these regions the tissue had a reticular, loose-meshed, vacuolated appearance, together with a great increase in the number of nuclei. The axis-cylinders did not stand out recognizably as they did in normal tissue.

In the carmine sections the cells involved in the *Abbau* process, not being differentially stained, did not stand out in their entirety. But the apparent reticulum contained a certain amount of granular material in the interstices, with here and there scattered groups of deep-staining homogeneous granules of varied sizes.

There was a great increase in the number of nuclei, which varied in shape and in the density of the chromatin. Nuclei typical of the astrocyte, of the microglia and less frequently of the oligodendroglia could be picked out, together with gradations that resisted classification.

Around many of the nuclei there was a certain amount of pink-staining cytoplasm. For the most part these cells were astrocytes, for, apart from the typical nucleus, the cytoplasm had the irregular, angular shape, with long rarely branching processes that seemed to merge in the

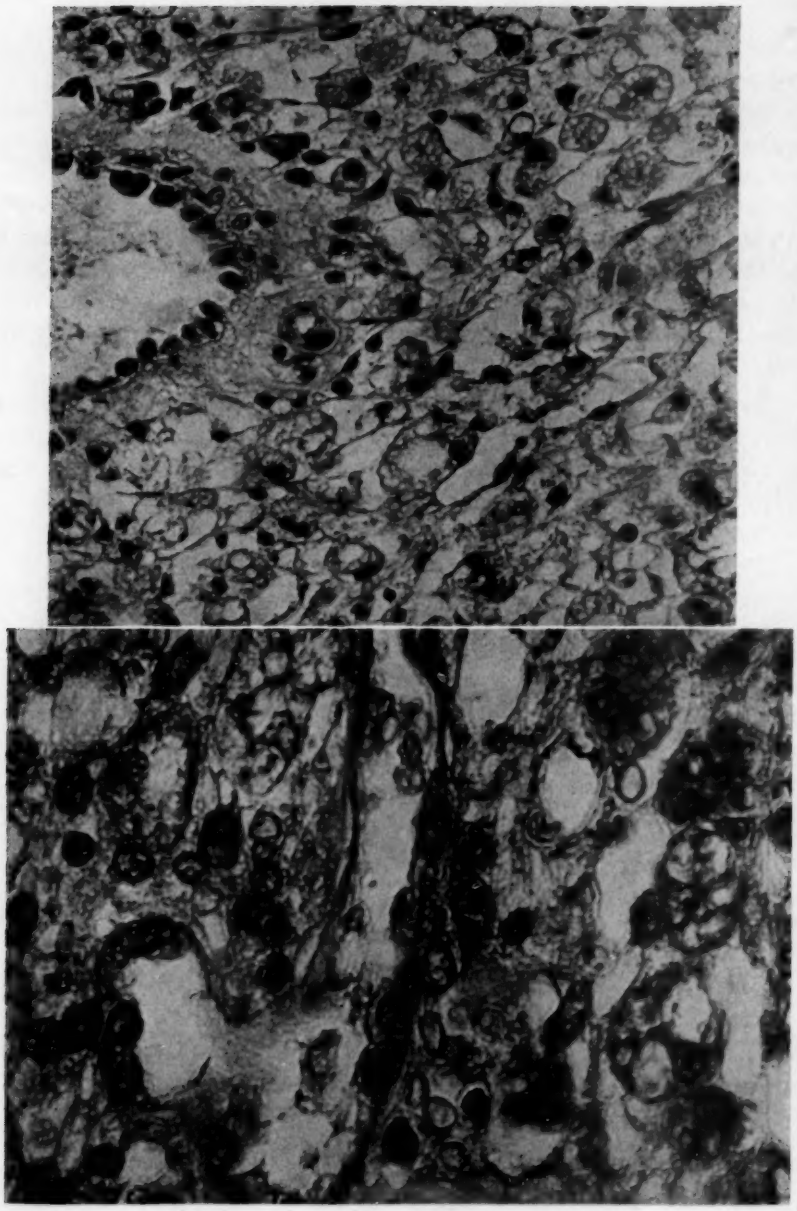

Fig. 4.—*A*, the same blood vessel as that shown in figure 3, about 0.5 mm. distant. The full extent of gitter cell formation from perivascular macrophages is shown. The cells contain large amounts of dustlike granules of trypan blue which are not visible in the photomicrograph. Note the swelling and rounding up of the endothelial cells. Paracarmine; × 350. *B*, transformation of capillary endothelium into wandering cells. The dark masses in cells to the right are large granules of trypan blue. The fine granules in the endothelial cells are not visible in the illustration. Paracarmine; × 750.

general syncytium. Mild hypertrophy was recognizable in these cells, as contrasted with the astrocytes in the normal white matter.

Around other nuclei there was occasionally a small amount of slightly granular cytoplasm, but this bore no resemblance to the

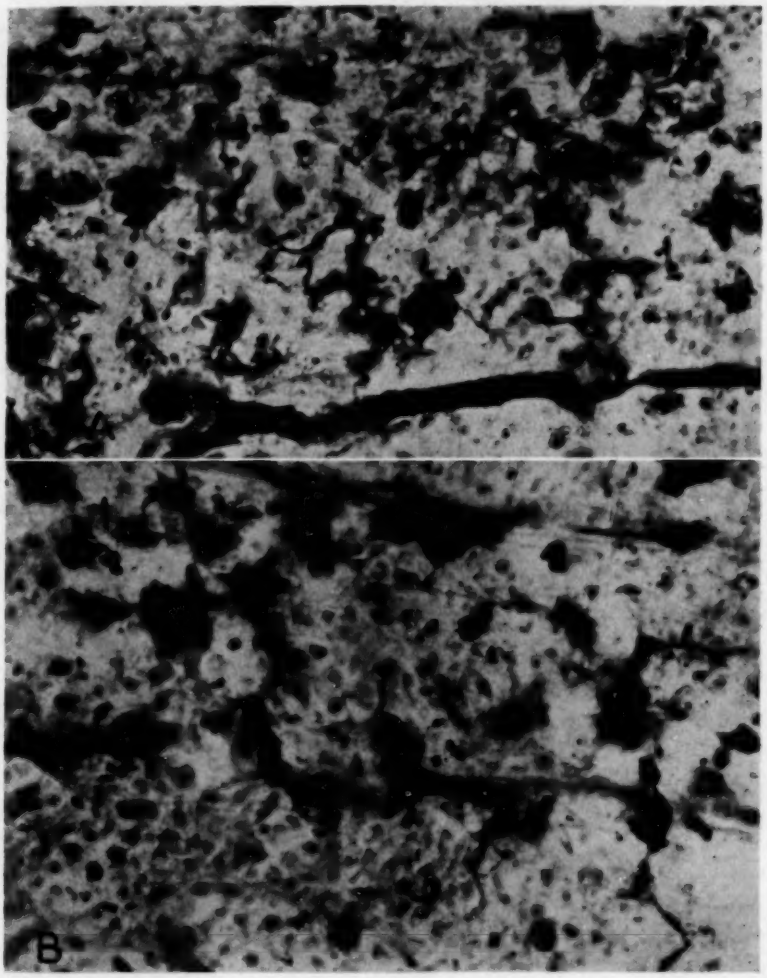

Fig. 5.—*A* and *B* show areas of secondary degeneration in the cervical region. Corresponding carmine preparations show no trypan blue. Silver carbonate; × 750.

astrocytes. In many cases these cells could be identified as microglia; in other cases identification could not be made. However, silver carbonate preparations (fig. 5) show the type of change which the microglia were undergoing. Figure 6 shows a lower magnification of a part of

the anterior horn from the same section shown in figure 5. It is inserted to illustrate the adequacy of the staining and the normal condition of the resting microglia. There is no need to enlarge further on the cytology of secondary degeneration, for it has already been worked out adequately.

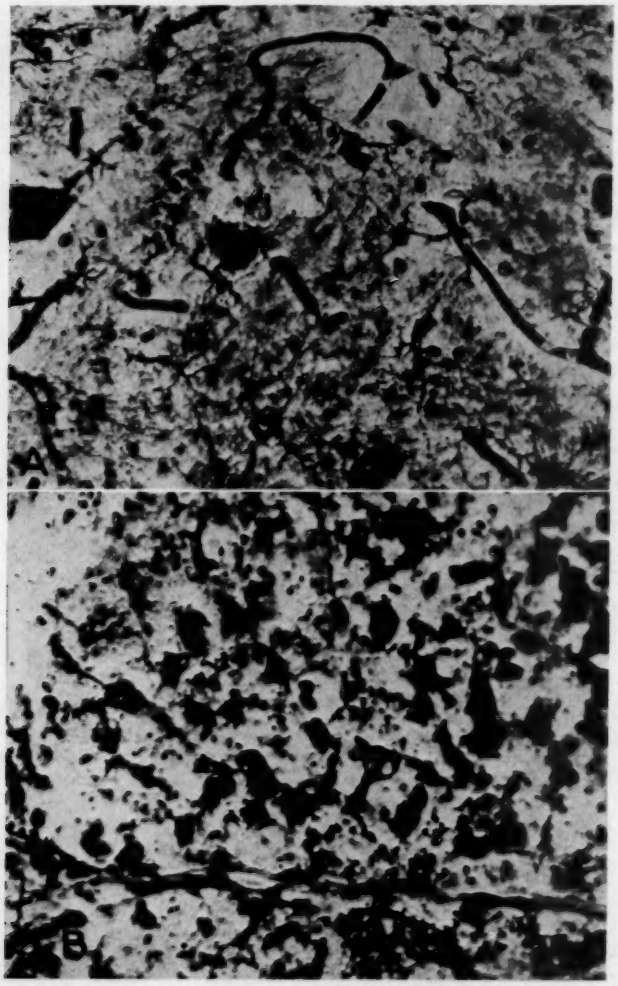

Fig. 6.—*A*, the anterior horn of the section from which figure 5*B* was taken, showing the nonactive microglia and oligodendroglia. Several neurons are heavily stained. Silver carbonate; × 280. *B*, microglia in the posterior columns about 1.5 cm. above the lesion. Corresponding carmine sections show a few granules of trypan blue. Silver carbonate; × 400.

There were only minute amounts of trypan blue in the cervical region. In every cord granules of dye were found in endothelial and adventitial cells of the blood vessels in the anterior and posterior median

fissures. The next most frequent locus of storage was around the blood vessels near the central canal. At those sites the dye was chiefly in the adventitial cells, occasionally in the endothelium. The granules were hard to find, and often several sections from the same block had to be examined before even a single granule was located.

Granules were also found in the capillary endothelium of vessels near the periphery of the cord, running radially. This was not true in all the cords, and it was extremely inconstant even when it did occur. For example, there might be a few granules, visible only with an oil immersion lens, in one section, while the adjacent section contained none. In any single section one or two fine granules in four or five different capillaries constituted a large number, encountered infrequently.

On the whole there was a slight tendency for more of the vitally stained endothelial cells to be located in the posterior half of the cord. Yet these cells did not stand in any constant relation to the degenerating tracts. My material does not warrant the conclusion that the degeneration of fiber tracts in the cervical region is accompanied by vital staining of the capillary endothelium within or bordering on such tracts, even though occasional instances of this phenomenon were found.

Glia cells in the cervical region were found to contain trypan blue only with the utmost rarity and not more often in the degenerating areas than in normal white matter or gray matter. Granules of dye were present in microglia and astrocytes in both normal and degenerating white matter and in microglia of the gray matter. But the extreme infrequency of such occurrences must again be stressed.

In the experimental animals the vital staining of the cervical region is perhaps slightly greater than that seen under normal conditions, but the total amount of dye is small and the distribution so inconstant that the significance of this observation is questionable.[5]

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5. The data of Rachmanow (Folia neuro-biol. **7**:750, 1913), described before the existence of microglia was known, are of considerable interest. He studied secondary degeneration in the spinal cords of rats and found no vital staining in the "ectodermal" elements (i. e., all types of glia). He did, however, observe staining in adventitial cells, and this was more marked in the area of degeneration than in normal tissue. He also described, as appearing in the stages between seven and ten days, rounded honeycombed cells, similar to myelophages except that they contained trypan blue. These, he claimed, were "polyblasts" wandering in from the vascular sheaths. He illustrated only a single isolated cell with dye granules, which is similar to the more vacuolated cells shown in my figure 3. Such dye-containing cells were not present after twenty days. (Nothing was said of the stages between ten and twenty days.)

These results are not in any sense confirmed by my experiments. In the cervical region of the cord in my animals the amount of dye was too slight to warrant the conclusion that more was present near the degenerating areas than elsewhere. The cell he figured was undoubtedly a "polyblast" similar to the more vacuolated cells

(Footnote continued on next page)

Intermediate Regions.—The regions of the cord intermediate between the cervical segments and the site of the lesion showed a certain amount of gradation between the two extremes. Preparations from the mid-dorsal region presented a somewhat heavier vital staining in the vascular endothelium and adventitia than did the cervical segments. Somewhat closer to the lesion the active glia cells in the degenerating zones in some specimens contained a few granules of dye, perceptibly more than in glia elsewhere on the slide. When this occurred the total amount of dye in the glia was nevertheless much less than in the perivascular macrophages.

The closer one approached the lesion, the greater was the proportion of the total white matter undergoing degeneration, and the more active the glia. Figure 6*B* illustrates, from a silver carbonate preparation, the type of glial reaction in the posterior columns about 1.5 cm. from the lesion. Here, in contrast to the cervical region, there was some trypan blue in the glia. This greater amount of degeneration was, of course, to be expected, since the fasciculi proprii were undoubtedly involved as well as the proximal ends of the long descending tracts.

COMMENT

Microglia and the Reticulo-Endothelial System.—The relation of the microglia to the connective tissue macrophages is a matter of extreme complexity and considerable dispute. The claim of Russell [6] that the microglia are "unequivocally" a part of the reticulo-endothelial system cannot be allowed to remain unquestioned. The microglia and the macrophages have many features in common, needless to enumerate, but the striking differences in their behavior to trypan blue cannot be neglected.

In normal animals on intravenous administration of dye the perivascular macrophages stain vitally with small doses; the microglia, only after prolonged and heavy doses.[7] In areas of inflammation the microglia

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(Footnote 5 concluded)

in my own figure 3. But such cells were not present in the cervical segments in my experiments. Moreover it is agreed that the (indubitable) mesodermal elements play no part in secondary degeneration of from seven to ten days' duration.

In view of Rachmanow's meager description and illustrations it is difficult to reconcile his results with mine. Other observations of his have not been confirmed by some of my unpublished data. For example, he claimed that in rats the pituitary gland is macroscopically unstained after administration of trypan blue. I have found the pituitary gland of rats to be colored an intense blue.

I do not know how to explain such a discrepancy in results. Possibly the dyes used, although bearing the same name, were quite different in character.

6. Russell, D. S.: Am. J. Path. **5**:451, 1929.

7. Mandelstamm, M., and Krylow, L.: Ztschr. f. d. ges. exper. Med. **58**:256, 1927.

store the dye, but not nearly so intensely as the macrophages. My own preparations show this difference strikingly. Macklin and Macklin [8] commented repeatedly on the heavy vital staining in macrophages as compared to that in the glia. Bolsi [9] more recently drew attention to this fact. The sparse staining in normal animals may possibly be explained by a hypothetic barrier; this explanation cannot apply to a focus of inflammation. When such a focus is present the dye is proved to have access to the tissue and to be equally available to all types of cells. Under these conditions a difference in storage relations between microglia and macrophages must necessarily be intrinsic and preexisting.

This difference may be only quantitative, it is true. But since the difference does exist, the term "unequivocally" as used by Russell must be modified.

Formation of Gitter Cells.—In an early work Farrar [10] claimed that all gitter cells in wound areas were derived from the vascular adventitia and the invading connective tissue. This was before the discovery of microglia as such. In recent times such gitter cells have been variously derived: They have been obtained from microglia, astrocytes, oligodendroglia, plasma cells, capillary endothelium and adventitial macrophages, according to different authors.

In the present experiments, in addition to the microglia, macrophages from the dura and the vascular adventitia were seen being transformed into gitter cells. Wandering cells derived from capillary endothelium rarely participated in this process. In some of the silver preparations many of the partially formed gitter cells seemed to be derived from oligodendroglia. Since there were no perivascular infiltrations, no statement can be made concerning the plasma cells. Nothing was ever seen to suggest the participation of astrocytes.

The gitter cell, when fully formed, is quite impossible to analyze into its parent cell type. Size may be a possible differentiating factor, for variation in this respect is well known.[8] In my preparations the cells which were certainly derived from macrophages were all large. But, although suggestive, this fact would not justify the converse statement that all large gitter cells have this origin.

All the gitter cells with large amounts of trypan blue are certainly derived from macrophages. This is only to be expected, since the order

8. Macklin, C. T., and Macklin, M. T.: Arch. Neurol. & Psychiat. **3**:353, 1920.

9. Bolsi, D.: Riv. di pat. nerv. **37**:13, 1931.

10. Farrar, C. B.: On the Phenomena of Repair in the Cerebral Cortex: A Study of Mesodermal and Ectodermal Activities Following the Introduction of a Foreign Body, in Nissl, Franz, and Alzheimer, Alois: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1908, vol. 2, p. 1.

of transformation is: The cells first are laden with trypan blue and then ingest fat. It has long been known, at least since the time of Doinikow, that when once laden with fat the macrophages do not aggregate trypan blue into granules. The cells which have ingested any quantity of fat cannot store as much trypan blue as similar cells free from lipoid inclusions. There is no reason to suppose that the microglia behave differently. As figure 2 illustrates, the microglia which take up relatively large amounts of dye show morphologic changes but contain little or no fat. In the white matter, where phagocytes contain large amounts of fat, the amount of trypan blue in the microglia is slight.

It is impossible to estimate, even approximately, the proportion of gitter cells which are derived exclusively from the macrophages. Nevertheless, the vascular adventitia and the connective tissue furnish a significant number of such compound granular corpuscles. This conclusion is intended to apply only to wounds and not necessarily to degeneration of myelin from other causes.

VITAL STAINING OF MICROGLIA

It is generally agreed that the resting microglia in the normal animal do not take up trypan blue. For such vital staining to occur the microglia must be activated. It has been pointed out that at the site of the lesion, and for a distance up to a few centimeters above it, the microglia, active in phagocytosis, may contain significant amounts of trypan blue. On the other hand, in secondary degeneration in the cervical region the microglia are morphologically equally active but do not contain trypan blue. How are these facts to be explained?

In neuropathology it is customary to distinguish sharply between inflammation and degeneration. Spielmeyer, with his concept of "symptomatic inflammation," [11] implied that the line of division may not be quite so sharp and that extensive breakdown of tissue, from whatever cause, may induce some inflammatory reaction. Nevertheless, without entering into controversial ground it is safe to say that secondary degeneration differs profoundly from a focus of inflammation.

In the present communication the spinal cords were described under three headings. At the site of the lesion, where vital staining of microglia was most intense, there was obviously a condition of inflammation. Above the lesion, for a variable distance, in the distal part of what I have called the intermediate region, the microglia stained vitally, though with diminished intensity. The reaction at those sites may have been an upward extension of the primary inflammation resulting from the injury, or it may possibly have been a secondary "symptomatic

11. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922. Yü-Lin, Ch'Eng: Arch. Neurol. & Psychiat. **31**:1247, 1934.

inflammation" due to the large proportion of degenerating tissue. For the purpose of the discussion either classification is satisfactory. Finally, in the cervical region there was "pure" secondary degeneration.

Microglia, then, which are active in an inflammatory focus, may stain vitally. When the activity occurs in secondary degeneration such vital staining is absent. It follows, therefore, that vital staining of microglia is dependent on the presence or absence of inflammation, not on the morphologic activity of the cells per se.

The exact changes inducing the inflammatory state are, unfortunately, not known. It is known, however, that the blood vessels become more permeable. One explanation for the behavior of microglia to vital dyes is along this line of vascular permeability, that is, according to the concept of the hemato-encephalic barrier. When the blood vessels are normal they do not allow trypan blue to pass into the tissues; consequently vital staining of the microglia is not possible, regardless of whether they are active or not. In a focus of inflammation, where the permeability is known to be raised, the dye passes the endothelial barrier. Vital staining then occurs.

However, a different explanation of the data is possible. One can assume that the capillaries in the brain do not differ from those in other organs and that vital dyes have access to all tissues equally. Instead of a barrier, one can postulate a lack of affinity or "binding power" in nerve tissue. This property must rest on some physical or possibly chemical basis as yet unknown.

In inflammation the factors which act on the blood vessels to make them more permeable must necessarily act simultaneously on all tissue elements. If these factors can change the properties of capillary endothelium they may also alter the affinity of parenchymatous elements.

Vital staining of microglia in a focus of inflammation may thus be the result of a "sensitization" (altered affinity) produced by the same factors which affected the blood vessels. In secondary degeneration, a noninflammatory condition, these sensitizing factors are absent. Consequently the microglia, though active, do not stain vitally because of their intrinsically low affinity together with their intense preoccupation with lipoid phagocytosis.

Either explanation involves a postulate not capable of direct proof: there exists either a barrier which may be broken down or an intrinsically low affinity which may be raised. At present it is impossible to decide which of these theories is correct. Either is fully adequate to explain the data here presented. The observed presence of trypan blue in microglia does not indicate by what mechanism the vital staining occurred. Some change from normal has been wrought, but whether this change is primarily in the blood vessels or in the cells cannot be decided at present.

CONCLUSIONS

1. The affinity for trypan blue is of a distinctly lower order of magnitude in microglia than in the macrophages of the central nervous system.

2. A significant proportion of the gitter cells in a wound area arise not from the microglia but from macrophages of the vascular sheaths and of the invading connective tissue.

3. Microglia far removed from a focus of injury, when stimulated to activity by the process of secondary degeneration, do not store trypan blue.

RELATION OF ALLERGY AND LESIONS IN ANIMALS VACCINATED WITH BCG

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MINNEAPOLIS

Much significance is attached to the relation of the allergic state to anatomic changes (lesions) in tuberculosis. The two chief aspects of the relation are the anatomic basis or cause and the anatomic results of allergy.

Krause [1] evidently had the first of these aspects in mind when he made the dictum, "there is no allergy without tubercle." Zinsser and Mueller [2] in discussing the cause of allergy wrote: "It appears that the development of typical tuberculin sensitiveness is not dependent upon the successive injection of dissolved bacillary extracts, which may be followed by antibody formation, but depends, rather, upon actual infection with the bacilli." They held the opinion that bacterial protein is broken up in a lesion so that the nucleoprotein is set free and stimulates the production of antibodies different from those due to the antigen in the whole bacterial cell. Bacterial hypersensitiveness (allergy), according to them, is due to the presence of antibodies developed against the nucleoprotein of the bacterial cells.

The anatomic results of allergy are of special significance in a consideration of the pathogenesis of lesions, especially in tuberculosis. It is now generally believed that necrosis in tuberculous lesions with an increased possibility of spreading the infection is dependent on the allergic state. Long [3] emphasized this when he stated that the opinion is growing that necrosis is largely the effect of the protein of the tubercle bacillus in a body made hypersensitive to the micro-organism by pre-existing tuberculous infection.

From experiments on sensitization with tuberculin protein Seibert [4] concluded that a high degree of hypersensitiveness to tuberculin protein on subsequent tuberculous infection seemed to hasten and extend the course of the lesions and to be associated with much more extensive necrosis and caseation than is found in nonsensitized animals.

From the Department of Pathology, University of Minnesota

1. Krause, A. K.: Tr. Nat. Tuberc. A. **17**:348, 1921.
2. Zinsser, H., and Mueller, J. H.: J. Exper. Med. **41**:159, 1925.
3. Long, E. R.: Am. Rev. Tuberc. **22**:467, 1930.
4. Seibert, F. B.: Proc. Soc. Exper. Biol. & Med. **30**:1274, 1933.

In referring to desensitization in tuberculosis Rothschild, Friedenwald and Bernstein [5] stated that it is well known that the hypersensitive state is responsible for the destruction of tissue and for the mechanical spread of infection.

The relation of allergy to the pathogenesis of lesions is considered in the present paper in the study of the relation of the allergic state in animals to lesions due to subsequent infection.

Another consideration to be taken into account is the significance of the production of allergy and lesions in the practice of vaccinating against tuberculosis with B C G or by other means. While carrying on experimental vaccination with B C G in rabbits the relation of allergy to lesions was studied. It was found that some of the animals became allergic while others did not. Animals inoculated subcutaneously with living B C G commonly became allergic, but those given intravenous injections of heat-killed B C G never became allergic. Following these observations it was decided to vaccinate rabbits by different methods and test for allergy and lesions in order to determine whether or not the lesions which could be found by gross or microscopic examination bore any relation to allergy from the standpoint either of cause or of effect.

METHODS AND MATERIALS

Rabbits were given injections of 1 mg. of finely ground B C G in 1 cc. of salt solution four times at weekly intervals. The injections were administered by the following four methods: (1) subcutaneously with living organisms (10 animals), (2) intravenously with living organisms (12 animals), (3) subcutaneously with heat-killed (60 C. for thirty minutes) organisms (10 animals) and (4) intravenously with heat-killed organisms (11 animals). The basis for the use of the four methods of injection was suggested by previous experiments [6] in vaccination with streptococci in which it was found that the intravenous method of giving the vaccine was superior to the subcutaneous method because allergy was not produced. This was true with both living and heat-killed streptococci.

The intracutaneous injection of old tuberculin (Mantoux test) was used for estimating the presence and the degree of allergy. One milligram of old tuberculin in a volume of 0.1 cc. was injected intracutaneously. In the rabbit's skin this gave an excellent wheal. When the tuberculin was injected intracutaneously in a dose of 0.05 mg. into a person positive to tuberculin, a strong positive reaction resulted.

The skin reactions in the rabbits were observed forty-eight hours after the injection of the tuberculin. The readings were recorded as varying from + to ++++. An induration at the point of injection of the tuberculin was required for any positive reading, and necrosis of the skin, for a ++++ reading. The Mantoux test was regularly made three weeks after the fourth injection of the B C G. It had been found by many previous tests that if allergy is not present by this time it does not appear later, following the described methods of vaccination.

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5. Rothschild, H.; Friedenwald, J. S., and Bernstein, C.: Bull. Johns Hopkins Hosp. **54**:232, 1934.

6. Clawson, B. J.: J. Infect. Dis. **53**:157, 1933.

In another series the animals were made allergic by subcutaneous injection of a single dose of 4 mg. of living B C G. After these animals became allergic they were given an intravenous injection of living or heat-killed B C G. Later they were killed and examined for lesions. The purpose of this experiment was to study the anatomic results of allergy from subsequent infection in allergic animals.

The degree of anatomic change resulting from vaccination or from later intravenous injections in animals already allergic was studied in many microscopic sections of the lungs, liver, spleen and kidneys. The severity of the lesions was recorded in grades ranging from + to ++++. Grade + represented only an occasional area of interstitial pneumonia or a small solitary epithelioid tubercle. Grade ++++ represented many tubercles or areas of intestinal pneumonia scattered thickly throughout the slides. Necrotic tubercles were practically never seen, and organisms were not found in stained sections of the lesions except in the subcutaneous lesion at the point of vaccination, where many organisms could be noted. The number and character of the lesions which developed from the subcutaneous injection when this method of vaccination was used were also noted.

RESULTS OF THE EXPERIMENTS

The experiments were first studied from the standpoint of the cause of allergy. Ten animals were vaccinated subcutaneously with living organisms. In each of them a subcutaneous lesion developed at the point of vaccination. The lesions ranged in size from 0.5 to 2 cm. in diameter. Microscopically, similar young lesions from other animals were found to be abscesses containing many polymorphonuclear leukocytes which had ingested numerous acid-fast bacilli. In older subcutaneous lesions the cellular exudate consisted primarily of macrophages, many of which also contained acid-fast bacilli, but the number of the organisms was greatly reduced, and the lesions were beginning to be walled off by fibroblasts. In none of the ten animals vaccinated subcutaneously with living B C G were any lesions found by gross or microscopic examination in the lungs, liver, spleen or kidneys. If the organisms had been dispersed from the point of subcutaneous injection, they had not been able to produce lesions in remote areas.

Allergy, indicated by a positive Mantoux test, was present in grade ++ to ++++ in all but three of the ten animals. In this group it was shown that, although allergy was not present in all of the animals, allergy did not occur except in animals which had lesions (in this group lesions were present in all).

In the twelve animals that received intravenous injections of living B C G it was noted that lesions were present in the lungs, liver and spleen in degrees of +++ and ++++ in the first four animals. In the next five animals lesions were found only in the lungs and only as + to ++. In the three remaining animals no lesions were found in any of the organs. No lesions were seen in the kidneys in any of the animals.

Allergy was observed, + to ++ degrees, in the first five animals. In none of these did the degree of the lesions in the lungs drop below

++. In the four animals in which lesions were found only in the lungs and only as +, no allergy was detected by the Mantoux test. Allergy was not present in the three animals with no lesions. In this group, as in the animals vaccinated subcutaneously with living B C G, allergy did not occur in any animals in which lesions were not detected. When few lesions were found and when they were confined to one organ there was no allergy. The highest degree of allergy was noted in the animals with the greatest number and degree of lesions.

In the ten animals vaccinated subcutaneously with heat-killed B C G, small lesions, similar in structure to those seen in the subcutaneous areas in the animals vaccinated subcutaneously with living B C G, were frequently but not always present. No lesions were found in the lungs, liver, spleen or kidneys in any of the animals. Allergy was present in three of the ten animals, twice as + and once as ++.

In this group, as in the two preceding groups, allergy was present only in animals which had lesions. Less allergy was noted than in the group of animals vaccinated subcutaneously with living organisms. The lesion at the point of injection was also smaller or absent.

No lesions and likewise no allergy were observed in the eleven animals vaccinated intravenously with heat-killed B C G.

In the four groups forty-three animals were inoculated by the four different methods for the purpose of obtaining a variation in the number and degree of lesions produced. In the forty-three animals allergy was never detected except in animals in which lesions could be found. In some cases lesions were present without allergy, but as a rule in these the degree of the lesions was slight and the lesions were found to be less extensive. The findings suggest a strong causal relation between lesions (cause) and allergy (result).

The effect of existing allergy on the development of lesions in allergic animals subsequently inoculated intravenously with living or heat-killed B C G is shown in table 1. In this group ten rabbits were selected. Five were made hypersensitive (allergic) by a subcutaneous injection of 4 mg. of living B C G. This amount injected subcutaneously never produced lesions in the visceral organs in control animals. Each of the five allergic animals and five of the nonallergic animals was then given an intravenous injection of 1 mg. of living B C G. The five animals which had previously received the sensitizing injection had ++ and +++ Mantoux readings. The five control animals showed negative results. Three weeks after the intravenous injection of living B C G the ten animals were killed and the organs examined for lesions. The five which had ++ and +++ Mantoux readings had +++ and ++++ grade lesions in the lungs, ++ and +++ grade lesions in the liver and + and ++ grade lesions in the spleen. As in previous experiments, no lesions were seen in the kidneys. In

two of the five control animals a + degree lesion was present in the lungs; the liver, spleen and kidney showed no lesions. In the three remaining control animals no lesions were present in any of the organs.

In table 2 experiments are reported in which similar results were obtained by inoculating allergic animals intravenously with heat-killed

TABLE 1.—*Results Obtained by Injecting 1 Mg. of Living B C G Intravenously into Animals Previously Made Allergic by a Subcutaneous Injection of 4 Mg. of Living B C G* *

Rabbit No.	Lesions				Allergy
	Lungs	Liver	Spleen	Kidneys	
Allergic animals					
1	++++	+++	++	0	+++
2	+++	+++	++	0	+++
3	+++	++	+	0	++
4	+++	++	+	0	++
5	+++	++	+	0	++
Nonallergic controls					
1	+	0	0	0	0
2	+	0	0	0	0
3–5	0	0	0	0	0

* The degree of the lesions and of allergy is indicated in tables 1 and 2 in grades ranging from + to ++++.

TABLE 2.—*Results Obtained by Injecting 0.25, 0.5, 0.5 and 0.5 Mg., Respectively, of Heat-Killed B C G Intravenously at Four Weekly Intervals into Animals Previously Made Allergic by a Subcutaneous Injection of 4 Mg. of Living B C G*

Rabbit No.	Lesions				Allergy
	Lungs	Liver	Spleen	Kidneys	
Allergic animals					
1	++	+++	0	0	+++
2	++	++	0	0	+++
3	+	0	0	0	+++
4	++	+++	0	0	++
5	+	0	0	0	++
6	+	0	0	0	++
Nonallergic controls*					
1–10	0	0	0	0	0

* Each control animal was given four intravenous injections of 1 mg. of heat-killed B C G.

B C G. The allergic animals were given four intravenous injections at weekly intervals of 0.25, 0.5, 0.5 and 0.5 mg., respectively, of heat-killed B C G. The ten control animals were given four similar injections of 1 mg. of heat-killed organisms. No lesions developed in any of the organs of the normal animals following the intravenous injection of the four doses of 1 mg. of heat-killed B C G; but when four injections of from 0.25 to 0.5 mg. of heat-killed B C G were given intravenously to animals which had previously been made allergic, lesions developed both in the lungs and in the liver. The six animals with allergy of grades ++ to +++ had lesions of grades + to ++

in the lungs. Lesions of grades ++ to +++ were found in the liver in three of the animals. No lesions were found in the spleen or liver in any of the six animals.

The results obtained from injecting intravenously either living or heat-killed B C G into allergic animals, when compared with the extent of lesions produced in normal animals given similar injections of equal or larger amounts, showed that the allergic animals were decidedly more susceptible to the development of lesions. The effect of allergy in accentuating the development of lesions in animals by subsequent infection is demonstrated in these experiments.

COMMENT

In the foregoing experiments the relation of allergy to the presence of lesions was studied in animals vaccinated with B C G. In the animals vaccinated so as to produce no allergy, lesions were few or absent, but in those in which allergy was developed lesions were always present. In a few cases lesions were present to a slight extent without allergy, but allergy was never present in animals in which lesions could not be found by gross or microscopic examination. Therefore, the belief in the causal relation between lesions and allergy was supported.

It was also found that when animals previously made allergic were given intravenous injections of living or heat-killed B C G in doses which seldom or never produced lesions in normal animals, extensive lesions developed. The allergic state in the animals seemed to cause a marked increase in susceptibility to the development of lesions. This hypersusceptibility to subsequent infection in the allergic animals suggests a possible relation of allergy to the pathogenesis of lesions in human tuberculosis.

SUMMARY

These experiments support the belief that without a lesion in tuberculous infection there is no allergy and that an allergic animal is more susceptible to the development of lesions from equal subsequent infections than a nonallergic animal.

Allergy did not occur at all in animals in which lesions were not found. An amount of living or heat-killed B C G which failed to produce lesions when injected intravenously into normal animals resulted in the production of extensive lesions in the lungs, livers and spleens of animals which had previously been made allergic.

ABSENCE OF CHEMOTROPISM IN LYMPHOCYTES

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AND
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It has been known for many years that polymorphonuclear leukocytes are attracted by bacteria and by certain other substances, this phenomenon being known as chemotropism, or chemotaxis. Whether lymphocytes likewise are attracted has long been a question. The fact that lymphocytes are found in inflammatory exudates has been taken by Askanazy [1] and others as evidence that they have been chemotropically attracted. But no one who has observed living lymphocytes under the microscope has, so far as we know, reported that these cells are attracted by bacteria or by other substances. Indeed, three reports have stated the contrary. Thus, Clark and Clark [2] observed that lymphocytes were not attracted by oil droplets, which had been injected into the tail of the tadpole. Maximow [3] studied the reactions of cultures of rabbit tissue to tubercle bacilli and found that lymphocytes showed no chemotropic response to the micro-organisms. Similar negative results were reported by Schade and Mayr,[4] who tested the attraction of drops of pus and of turpentine for human white blood cells in vitro. In these three investigations, though lymphocytes exhibited no response, other types of white blood cells were attracted by the foreign material.

While studying the chemotropic reaction of polymorphonuclear leukocytes in vitro, as recently reported,[5] we observed that lymphocytes did not appear to be attracted to the various substances employed. To obtain more precise information as to the reaction of lymphocytes, we decided to record their paths as they move in proximity to bacteria and to analyze the paths so as to obtain a numerical expression for their prevailing direction, whether toward or away from the bacteria. In

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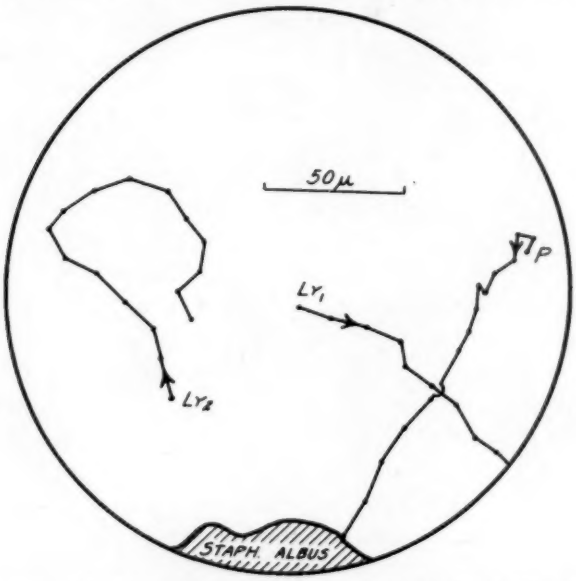
This investigation was aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

1. Askanazy, M., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, vol. 13, p. 317.
2. Clark, E. R., and Clark, E. L.: Am. J. Anat. **46**:149, 1930.
3. Maximow, A. A.: J. Infect. Dis. **34**:549, 1924.
4. Schade, H., and Mayr, K.: Krankheitsforschung **8**:378, 1930.
5. McCutcheon, M.; Wartman, W. B., and Dixon, H. M.: Arch. Path. **17**: 607, 1934.

the following experiments this method has been used to measure the reaction of lymphocytes of human blood to tubercle bacilli and to staphylococci.

METHOD

A minute clump of bacteria from an agar slant was placed on a glass slide and allowed to dry. Thus a flat, circular or oval body from 50 to 150 microns in diameter was obtained. A drop of blood from the finger-tip was placed on a coverslip, lowered onto the bacterial clump and allowed to spread between the slide and the coverslip. The preparation was sealed with petrolatum and examined with the oil immersion lens of the microscope in a warm box at 37 C. By means of a drawing ocular, the image of a microscopic field near the bacteria was projected onto a piece of paper, and the position of each lymphocyte and polymorpho-



This is a camera lucida record of the path of a polymorphonuclear leukocyte (P) and the paths of two lymphocytes (Ly_1 and Ly_2) during a period of nine minutes. Arrows indicate the direction of migration. It is seen that the polymorphonuclear leukocyte moved toward the group of staphylococci, whereas the lymphocytes did not appear to be attracted by the bacteria.

nuclear leukocyte was recorded at minute or half-minute intervals, usually for ten minutes. Thus, a record was obtained such as is shown in the figure. It is seen that the polymorphonuclear leukocyte moved in an almost straight line to the bacterial mass (Staphylococcus albus), whereas the lymphocytes appear to have moved at random.

Rarely were more than one or two lymphocytes found in one field. It was necessary, therefore, to examine many fields, each at a known distance from the bacterial clump. In each field the paths of the lymphocytes (if any) were recorded as well as those of the polymorphonuclears. At a distance greater than from 2 to 4 mm. from the bacterial clump, polymorphonuclears are not as a rule strongly attracted to bacteria; consequently, fields at a greater distance were not used. In compiling the data only those fields were charted in which the poly-

morphonuclears moved toward the bacteria, i. e., the fields in which the cells showed positive chemotropism.

The chemotropic response of each cell was measured by determining how nearly straight a path it took as it approached the bacteria. This was done by dividing the net distance it approached the bacteria by the total path traversed in the same time.[6] It is evident that if a cell moves in a straight line toward the bacteria, the net approach and the total path are identical and the ratio is +1; this is the maximal positive chemotropism. Conversely, if a cell moves in a straight line away from the bacteria, a ratio of —1 is obtained; this is the maximal negative chemotropism. For any experiment or group of experiments a mean value of the ratio for the two kinds of leukocytes may readily be found.

The observations were made at various times, from one-half to five hours after the preparation was mounted. As stated in a previous paper,[7] several hours pass before all the lymphocytes are in active motion. Therefore, when early readings were made, not all the lymphocytes could be included. Only small lymphocytes were observed, since large lymphocytes are difficult to identify in unstained preparations. The criteria used in identifying small lymphocytes have been previously described.[7] All experiments were made with the blood of one supposedly healthy man.

RESULTS

In the experiments recorded in the table, Staphylococcus albus and tubercle bacilli (bovine III strain) were used as sources of attraction, five experiments being made with each. Altogether the paths of 76 lymphocytes and of 96 polymorphonuclear leukocytes were measured.

As recorded in the table, the polymorphonuclears were strongly attracted by both kinds of micro-organisms. In the case of the staphylococci, the ratio of the net approach to the total path had a mean value of + 0.65; when tubercle bacilli were used the mean ratio was + 0.58.[8]

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6. This calculation will be illustrated by two examples. In the figure is a record of the path traversed by cell *P*, a polymorphonuclear leukocyte. When first observed this cell was 120 microns distant from the edge of a mass of tubercle bacilli. At the end of nine minutes the cell was in contact with the bacilli, having made a net approach to the bacilli of 120 microns. During this time it traveled a total of 140 microns, as may be seen if one measures the path recorded. The ratio of the net approach to the total path is $\frac{+120}{140}$, or +0.86. The lymphocyte designated Ly_2 in the figure was 46 microns distant from the bacteria at the first observation and 72 microns at the last, so that its net approach was —26 microns. During this time its total path was 179 microns. The ratio of these distances, $\frac{-26}{179}$, is —0.15.

7. McCutcheon, M.: Am. J. Physiol. **69**:279, 1924.

8. The mean values of the chemotropic reaction for the polymorphonuclears were lower than those reported from earlier experiments.[9] The chief cause for this difference was that in the earlier experiments all the cells charted were in the same microscopic field as the attracting bacteria, whereas in the present experiments, for reasons already given, many of the cells charted were at a greater distance from the bacteria and hence were less strongly attracted.

9. McCutcheon, M.; Dixon, H. M., and Krumbhaar, E. B.: Am. J. Path. **10**: 678, 1934.

With the lymphocytes, the results were quite different (table). When staphylococci were used as the source of attraction, the mean ratio of the net approach to the total path was zero; that is, the chemotropism was equal to zero, locomotion being entirely at random. With tubercle bacilli, the mean value of the chemotropism was —0.1; that is, the average movement of the lymphocytes was slightly away from the bacteria. However, it is evident from the standard deviation (0.43) that the mean value of the chemotropism (—0.1) was not significantly different from (0) random movement. It is therefore concluded that the lymphocytes were neither attracted nor repelled by Staphylococcus albus and tubercle bacilli.

A smaller number of observations were made with Staphylococcus aureus, Micrococcus tetragenus and typhoid bacilli. No evidence of attraction of the lymphocytes was found.

The Mean Values of the Chemotropic Response of Lymphocytes and of Polymorphonuclear Leukocytes as Determined in Ten Experiments *

	Lymphocytes		Polymorphonuclears	
Micro-Organism	Chemotropism	No. of Cells	Chemotropism	No. of Cells
Staphylococcus albus.....	0.00 ± 0.43	45	+0.65	60
Tubercle bacilli.....	—0.10 ± 0.43	31	+0.58	36

* From the mean ratios and the standard deviation it is seen that the chemotropic response of the lymphocytes is not significantly different from zero, random movement. The corresponding figures for the polymorphonuclears indicate positive chemotropic reactions.

The rates of locomotion of the lymphocytes and of the polymorphonuclear leukocytes were computed in the experiments in which tubercle bacilli were used as the source of attraction. For 29 lymphocytes the mean rate of locomotion per minute and the standard deviation were 13 ± 4 microns; for 32 polymorphonuclears, the values were 33 ± 8 microns. More extensive data on the rate of locomotion of lymphocytes [7] and of polymorphonuclear leukocytes [10] have been given in earlier papers. The most complete studies on lymphocytic motility are those of Lewis and Webster [11] and of Lewis.[12]

COMMENT

It is an interesting observation that of these two kinds of cells, the polymorphonuclear leukocyte and the lymphocyte—cells which are reported as having the same mechanism of locomotion [13]—observed side by side under identical conditions, the one exhibits chemotropism and

10. McCutcheon, M.: Am. J. Physiol. **66**:180, 1923.
11. Lewis, W. H., and Webster, L. T.: J. Exper. Med. **33**:261, 1921.
12. Lewis, W. H.: Bull. Johns Hopkins Hosp. **49**:29, 1931; **53**:147, 1933.
13. Lewis, W. H.: Bull. Johns Hopkins Hosp. **55**:273, 1934.

the other does not. Since our results are supported by those reported by others [14] who have watched living lymphocytes under the microscope, the weight of evidence seems to indicate that lymphocytes do not display chemotropism. Phagocytosis, also, as is well known, is not a function of lymphocytes (unless occasionally), and this seems reasonable since chemotropism, phagocytosis and intracellular digestion, or removal of foreign bodies, are successive stages of a complex function—one possessed by polymorphonuclears and macrophages but not, apparently, by lymphocytes.

The results here reported suggest the following questions: Is it possible to explain the difference in the chemotropic reactivity of these cells by differences in the cell surface? [15] By what mechanism, if not chemotropism, are lymphocytes accumulated in exudates and areas of inflammation?

SUMMARY

Leukocytes of human blood (lymphocytes and polymorphonuclear leukocytes) were observed under the microscope while moving near a clump of bacteria. The records made of their paths were analyzed in order to obtain a numerical expression for the prevailing directions, whether toward or away from the bacteria.

Lymphocytes were found not to be attracted by staphylococci or tubercle bacilli. Under the same conditions, polymorphonuclear leukocytes were strongly attracted.

Neither in these experiments nor in the literature has direct evidence been found that lymphocytes exhibit chemotropism.

14. Clark and Clark.[2] Maximow.[3] Schade and Mayr.[4]

15. For example, Abramson reported zeta potentials of different magnitude for polymorphonuclears and lymphocytes (Abramson, H. A., in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, New York, Biological Laboratory, 1933, vol. 1, p. 92).

Laboratory Methods and Technical Notes

STEREOSCOPIC PHOTOGRAPHY OF PATHOLOGIC SPECIMENS

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It has long been our opinion that the ordinary photography of pathologic specimens leaves much to be desired. No matter how clear the picture, much of the detail cannot be seen, and the anatomic arrangement is especially vague. In no type of photograph are the deficiencies of a flat plate more evident. In reducing the object to two dimensions the effect of solidity is gone, and with it many of the most striking pathologic characters.

The ideal record of such specimens is, of course, their preservation in proper fixing fluids, so that all of the natural colors are maintained. No worker in this field need be reminded that this is an expensive and time-consuming task. Unless the utmost care is taken, the specimen shrinks and bleaches, and in any case the mere housing of the collection becomes a problem.

It seemed desirable, therefore, that some method should be available for making a graphic record which should at the same time be convincing, compact and inexpensive. We were thus led to consider the application of stereophotography to this field. Its use in the "Edinburgh Stereoscopic Atlas of Anatomy" [1] shows the great advantage of creating the illusion of depth. We were of the opinion that it had never been adequately used in recording the appearance of specimens in pathologic anatomy.

We were, however, confronted with the fact that a camera suitable for such work was not on the market. A few trials with stereoscopic cameras of the ordinary type showed that they are inadequate. The chief objection is that the object has to be placed at least 1 meter from the lenses in order to be visible on each side of the plate. Thus the size of the image is too much reduced and the detail is not evident. The effect is that of looking at the specimen from across the room.

Power and Hala [2] recommended strereophotography of pathologic specimens but advised the use of one camera on a sliding frame. The negatives were to be exposed from different angles and later combined. The work of these men came to our notice after we had purchased our equipment and begun the work. We had considered such a procedure but had rejected it for the following reasons:

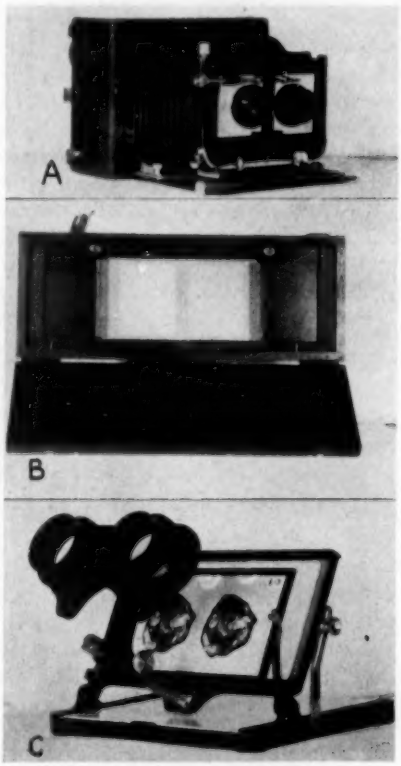
From the Department of Pathology, Iowa Methodist Hospital.

1. Waterhouse, D., editor: The Edinburgh Stereoscopic Atlas of Anatomy, Edinburgh, T. C. & E. C. Jack, 1906.

2. Power, H. D'Arcy, and Hala, W. W.: Principles of Pathology for Practitioners and Students, New York, D. Appleton and Company, 1929.

The method takes much more time and cannot result in as good a picture, for when seen in stereoscopic view each side must have exactly the same exposure. This is practically impossible unless the views of the two sides are taken at the same time. Also, an error in alining the sides results in evident imperfection, and, finally, such a method is not adapted to the photographing of lesions of the living patient.

After considerable correspondence on the subject with various firms, we submitted our problem to Mr. Herbert Pels of New York, an expert photographer, who has also had experience in stereoscopic work. He



A, stereoscopic camera; *B*, transposing frame, and *C*, Zeiss stereoscope.

advised the construction of a special camera and supervised its making in the workroom of the Adam Archinal Corporation of that city.

The camera thus devised has several advantages. Accurate focusing is possible. The lenses are movable laterally. Thus views can be taken within a distance of 9 inches (22.86 cm.). The lens board has vertical and horizontal adjustments and an extension bed. The camera is equipped with a focal plane shutter with speeds ranging from one-tenth to one-thousandth second. The lenses are matched protars, made by the Bausch & Lomb Company, with a focal length of 6.3 mm. Details of the camera may be seen in the figure.

The camera when in use is mounted vertically on a tripod directly above a sheet of plate glass supported on a frame. A dull black background is placed on the floor about 1 foot (33.02 cm.) beneath the glass. Two Kodaflectors are placed about the specimen so as to secure an even, flat illumination, which is finally controlled by focusing on the ground glass of the camera. Diffusing screens may be used to reduce the high lights caused by the blood or mucus on fresh specimens. Photographing specimens under a liquid medium, such as water or kerosene, has been found unsatisfactory. The specimen is carefully blotted with a towel to remove the excess fluid. It is then arranged on the plate glass so as to present the desired view, and in certain cases several views from different angles are taken. The whole procedure takes only a few minutes.

Eastman Portrait Panchromatic films, 3¼ by 5½ inches, are used for the negatives. The transparencies are printed on Eastman Commercial films of the same size. Positive film was found to give too marked a contrast.

Stereoscopic films must be reversed in printing. The physical theory is explained in the standard works on the subject.[3] For this purpose a transposing printing-frame is necessary (*B* in the figure).

The use of this kind of printing-frame permits prints or transparencies to be made without cutting the picture or remounting. Contact prints may be made, and these require no further mounting. Transparencies are superior, however, and these are bound between lantern-slide cover glasses cut to size.

For viewing the photographs, a Zeiss stereoscope, *C* in the figure, is recommended. Although a cheaper type may be used, a fine instrument like this is of great advantage.

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3. Judge, A. W.: Stereoscopic Photography, London, Chapman & Hall, Ltd., 1926.

Case Reports

RENAL ADENOSARCOMA IN A WHITE RAT

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A male white rat (Rattus norvegicus albinus) about 1½ years old, from a breeding colony, had a large tumor in the left flank and was killed as control material in current studies on the etiology of cancer.

At autopsy there was a large bean-shaped mass 5 by 3 cm. in diameter in the region of, and apparently including, the left kidney. The capsule was smooth, thick, fibrous and richly vascularized. On section the cut surface showed pearl-gray homogeneous areas and larger hemorrhagic, centrally necrotic areas without evident suppuration. Careful search of the other viscera revealed no other tumors or lesions.

Only the tumor was saved for histologic study. Four blocks of an area of from 3 to 4 sq. cm. were fixed in Orth's fluid and two smaller blocks in Hermann's platinic chloride-osmic acid solution.

On histologic examination a few small marginal areas of sparsely cellular fibrillar connective tissue staining yellow with picrofuchsin and enclosing a few small tubules and anemic adult glomeruli were observed. This tissue merged insensibly into the tumor proper.

The tumor was complex in structure and contained wide sinusoidal blood spaces; delicately fibrous, rather broad trabeculae, and areas of hemorrhage and necrosis. The most characteristic feature was the presence of masses of closely packed small cells with narrow cytoplasm, indistinct cell membranes and rather large, pale leptochromatic nuclei. These masses often surrounded well formed tubules composed of larger columnar cells with basally placed nuclei and hyaline or vertically striated cytoplasm. Gradations from these enclosed tubules to the dense mesenchyme-like cell masses surrounding them were, at most, rare. These mesenchyme-like dense cell masses usually frayed out peripherally into spindle and star cells in a myxomatoid matrix. In places there was a hyaline, faintly oxyphil matrix suggesting serous coagulum, which was traversed by a delicate wide-meshed net of narrow fusiform cells lying in anastomosing strands. The dense mesenchyme-like masses also formed rounded lumens in some, and these graded into irregular tubular structures composed of low cuboidal cells with scanty cytoplasm and nuclei indistinguishable from those of the solid masses. Such tubular structures sometimes contained one papillary ingrowth or more composed of the same cuboidal cells. Definite connective tissue or vascular cores in these papillae were not identified. Such structures possibly represent rudimentary glomeruli.

No cartilage or bone or smooth or striated muscle could be found in any of the sections.

From the National Institute of Health, United States Public Health Service.

The tumor apparently belongs to the group designated by Ewing [1] as embryonal tumors of renal blastema and may be called adenosarcoma, though mitotic figures were rare. In none of the fifteen cases of spontaneous renal tumors in rats collected by Jaffé [2] from the literature was the growth of this type.

In more than thirty-three thousand autopsies on white rats, Bullock and Curtis [3] observed six embryonal carcinomas of the kidneys, three of the left kidney and three of the right. The oldest animal was 640 days old, the other five ranging from 152 to 322 days in age. In addi-

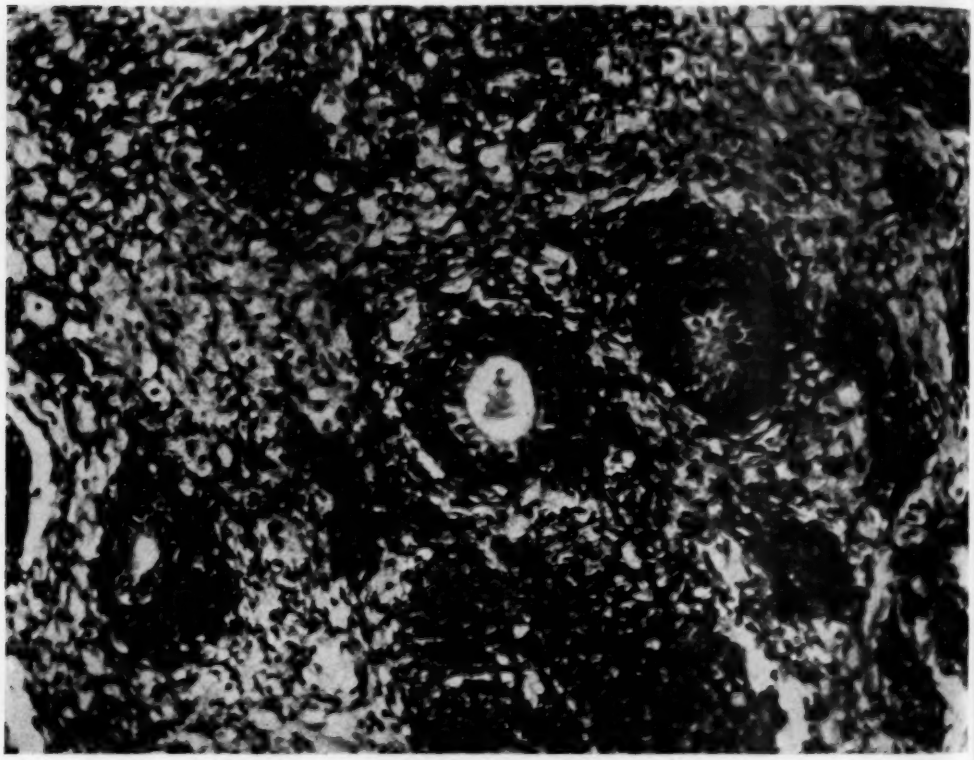

Fig. 1.—Section of renal adenosarcoma in the white rat; (magnification, ×230, as reduced ½). This photomicrograph was taken at the Army Medical Museum with the permission of Maj. V. H. Cornell, curator.

tion, they saw one adult adenocarcinoma and one sarcoma. One of their embryonal tumors (R172) contained striated and smooth muscle, was largely sarcomatous and showed only few attempts at tubule formation.

1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 796.

2. Jaffé, R.: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere, Berlin, Julius Springer, 1931, p. 757.

3. Bullock, F. D., and Curtis, M. R.: J. Cancer Research **14**:1, 1930

One (R474) was largely composed of spindle cells with whorls, nodules and infrequent small acini, tubules and abortive glomeruli, while another (R501) was similar except that no glomeruli were seen and there was extensive necrosis. The other three, typified by R91, were similar to each other and were apparently more like our tumor. There were compact masses of darkly stained, poorly outlined cells with relatively large spheroidal nuclei. These masses often enclosed well defined tubules or nests or cords of lighter-staining cells. Various stages of differentiation from the cell masses to the tubules were observed. Glomerulus-like structures were seen. The stroma was a very vascular edematous fibrillar tissue with many fusiform, oval and round cells which usually stained less deeply than the cell masses. Cords and nests of, and cysts lined with, transitional epithelium were seen. Mitoses were numerous.

General Review

MODERN ATTITUDE TOWARD TRAUMATIC CANCER

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Many recent fundamental contributions on the causation of tumors have an important bearing on the relation of trauma to cancer. When nothing definite was known about the effective exciting factors in mammary cancer it was permissible to adopt the traumatic theory in cases in which the clinical evidence pointed strongly that way. Now that it is known that one can produce mammary cancers in mice almost at will by overstimulation with theelin, whereas no one has succeeded in producing this disease by trauma, the traumatic origin becomes much less acceptable. Cancer has now been produced experimentally by many agents, but always under specific conditions that are not related to trauma, and the experimental data reveal the fact that the genesis of cancer requires quite peculiar factors which have not been found in the results of simple trauma.

The newer revelations regarding the physiologic significance of tumors cannot fail to modify views concerning their possible relation to simple traumas. At one time it seemed necessary to assume that many cases of giant cell tumor of bone resulted from injury, but since it has appeared that this disease is related to a functional disturbance of the parathyroid gland, and that giant cell tumors may be produced by hyperparathyroidism and cured by extirpation of tumors of the parathyroid glands, it becomes unnecessary to introduce the idea of trauma into the etiology of giant cell tumors. The application of di-benzanthracene to experimental animals produces cancer and sarcoma promptly and almost invariably, whereas the innumerable efforts to cause tumor by simple trauma have always failed. This contrast cannot fail to impress thoughtful observers with the fact that when one deals with real cancerigenic agents the results are definite, positive and even startling, and that the negative results of traumatization indicate that a trauma does not possess the essential elements of a cancerigenic agent. Knox [1] has reviewed many of the old and recent efforts to produce tumors by traumatization, all of which have failed.

These and many other contributions of the past two decades have greatly widened the breach between the real causation of malignant tumors and the theory that they may be caused by single trauma, and these new facts must be fully considered in forming opinions regarding

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases

1. Knox, L. C.: Arch. Path. **7**:274, 1929; Am. J. Surg. **26**:66, 1934.

the traumatic origin of any given tumor. However, the new facts do not warrant the exclusion of trauma as a possible cause of many tumors. The clinical evidence is too substantial in many cases to be dismissed on theoretical grounds. Recent knowledge demands merely that the evidence favoring trauma must be scrutinized more closely and great importance must be given to other factors which are more in line with the causes known to be effective in exciting neoplastic growth.

While it is now generally agreed that a single trauma never produces a malignant tumor in previously normal tissue, this principle may not greatly reduce the medicolegal importance of an injury as an indirect cause of a tumor. When a lacerated wound of the skin with implantation of foreign material fails to heal, becomes infected and suppurates for weeks or months, and cancer finally appears in the edges, it is clear that the cancer would not have occurred without the trauma.

ESSENTIAL CHARACTERS OF MEDICOLEGAL EVIDENCE

One of the chief difficulties in the estimation of the frequency of traumatic cancer is the uncertainty of the statements of interested patients. Juries and compensation courts may accept the statements of claimants at face value, but medical science cannot indulge sympathies or make loose assumptions. To have medicolegal value, the statements of claimants must be supported by circumstantial evidence. Even the assertions of eye-witnesses, which have a certain corroborative value, cannot be accepted as facts unless supported by circumstantial evidence. There have been many striking instances of the positive assertions of several eye-witnesses being proved wrong by circumstantial evidence which was inconsistent with such statements. For example, a man was seen by several nearby persons to run out of a saloon, followed immediately by an assailant, who stabbed the victim in the back with a knife. The assailant was tried for murder but acquitted because the autopsy disclosed that the victim had died of a deep wound of the liver, delivered from the front, while the observed knife wound had barely penetrated the skin of the back.

Therefore, all statements of claimants and eye-witnesses regarding accidents should be supported by concrete, readily verifiable evidence relating to the locality of the accident, the objects alleged to have been concerned and the possibility of the occurrence of the injury described. If such necessary evidence were secured, the number of reports of traumatic cancer in the literature would be enormously reduced.

Without attributing to any claimant a deliberate intention to falsify the facts, every student of psychology knows that the human mind is strongly influenced by preconceived notions and by self-interest. The wish is father to the thought. By repeatedly asserting things of which

the mind is at first uncertain, it is possible to convince the mind of the reality of incidents that have not occurred. At any rate, for scientific purposes, this law of psychology must be regarded in all inquiries concerned with the traumatic origin of tumors. When the patient's doctor, on whom the patient's life may depend, begins an inquiry with a display of interest in establishing a history of trauma the patient invariably responds with a vivid imagination, and the doctor himself becomes a victim of his own efforts. Even the most judicially trained minds are not free from this subtle influence. When the United States Supreme Court, in 1876, was called on to decide whether Samuel J. Tilden or Rutherford B. Hayes had been elected president, the evidence consisted of certain verifiable facts, but the four Republican members voted in favor of Hayes, and the three Democratic members voted for Tilden.

Having investigated many cases in which the statements of the patient and his friends clearly indicated a traumatic origin of a tumor, only to find that these statements were unreliable, I have become convinced that the chief task of the medicolegal expert is not one of theoretical reasoning and argument but almost entirely one of laborious fact-finding. It requires time, patience and ingenuity to establish the facts in a case of tumor alleged to be traumatic, and unless these efforts are competently made, the report of the case is, for scientific purposes, worthless:

An intelligent young woman, free from any thought of compensation, presented herself at the Memorial Hospital for the Treatment of Cancer and Allied Diseases with the following history: In August 1934 she stated that she had fallen out of a swing and struck violently on a gravel bed, bruising the palm (but not the wrist?) of her right hand. She paid little attention to the incident. One month later she noticed that the fingers of the right hand were contracting, and this condition became steadily worse until November, when she went to an orthopedic hospital, where Dupuytren's contraction in a pronounced form, with marked nodular thickening of the whole palm, was found. The palmar fascia was then liberally excised. On section the material showed a cellular neurogenic fibrosarcoma of considerable malignancy, tumor cells infiltrating the nerve trunks throughout. She stated that before the accident the hand was entirely normal, because she was able to use the typewriter in her occupation without difficulty. Here was a most circumstantial and convincing story pointing clearly to a traumatic neurogenic fibrosarcoma: 1. The previous integrity of the tissues was adequately shown by the lack of interference in using the typewriter. 2. The authenticity of the trauma was well established by the violent fall under unusual conditions, which she stated was witnessed by 3 friends. 3. The nature, probable age and active growth of the tumor completely coincided with the story.

However, it was determined to make a systematic effort to break down the assertions in the story, and 2 physicians devoted several hours to the task. It required 3 interviews to prove that the account of having fallen out of a swing was a fiction. To one interrogator she failed to mention the swing and referred the trouble to overuse of the broom. She had just been separated from her hus-

band, and he could not be found. Her brother-in-law was in camp in Canada (December 15?) and could not be reached, and her "sister-in-law" (who should have been her sister) was with him. Thus none of the alleged witnesses could be reached. She finally admitted that she had not used the typewriter for three years. A review of new sections from other parts of the tumor material revealed much old hyaline fibrous tissue that was completely devoid of cells, which must have existed much longer than the three months' alleged duration of the tumor.

PROBABILITY OF COINCIDENCE OF TRAUMA AND CANCER

Assuming that every tumor that arises after trauma is of traumatic origin, one still finds the incidence of traumatic tumors extremely low. In the records of the New York State Industrial Compensation Bureau, Lewy found that 37 malignant tumors had occurred among 26,389 injured persons. In few of these cases could the claim of a traumatic origin be established as reasonable. This incidence is about the normal incidence of tumors among the general population. Some French medico-legal experts reported the occurrence of as few as 5 or 6 traumatic tumors among 100,000 injuries. Many authors have remarked on the very small number of traumatic tumors observed during the Great War (Knox [1]). According to von Bunganer (cited by Ullmann [2]), in all the German University clinics during a long period of observation, not more than 100 certified traumatic tumors have been recorded. From these data one must conclude that trauma itself has generally very little tendency to produce a malignant reaction in tissues and that when it does so the conditions must be peculiar.

Not only those persons who acquire supposedly traumatic tumors, but all classes of the population, especially young persons and artisans, are constantly exposed to injuries, mild and substantial, to which they pay no attention. The National Safety Council reports that in the United States there were, in 1933, 8,730,000 disabling injuries. There must have been many more of milder type, the type to which tumors are generally referred. The skin, the bones and the female breasts are especially exposed to injuries. There is thus established a strong probability that by mere coincidence any portion of the body in which a tumor develops has at a recent date received a blow. Yet this argument loses some force when it appears that a tumor developed shortly after an unusual injury and at the exact point of injury.

The probability of coincidence becomes more clearly revealed when one considers the factor of time in the development of cancer. Cancer does not develop suddenly. The precancerous changes cover a period of months and sometimes years before the signs of established disease appear. During all this time the tissues are exposed to the usual

2. Ullmann, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, chap. 3, p. 551.

traumas, mild and severe, to which the average person in active life is subjected. If at any time during this long period a trauma occurs at the site of the precancerous lesion, the subsequent cancer may erroneously be attributed to the trauma, whereas it is the inevitable result of the progress of precancerous changes which had nothing to do with the trauma.

The coincidence of two very rare events raises a presumption but does not prove that there must be a causal relation between them:

A man fell backward on a cellar floor, fracturing the spinous process of the seventh cervical vertebra. Two months later he complained of a nodular thickening along the brachial plexus and marked atrophy of the muscles of the hand. A slowly growing fibrosarcoma of the brachial plexus was disclosed, which ran its course in three years. The previous history could not be established, but it is reasonably certain that the tumor antedated the injury, for this was limited exactly to the spinous process, and the latter healed normally.

Here the coincidence of 2 rare events created a presumption of a causal relation. A positive opinion could not be given because of imperfect fact-finding, especially in regard to the previous condition of the patient, the immediate neurologic effects of the injury and the exact date of appearance of the atrophy.

A child was run over by an automobile, the wheel passing over the pelvis. He was taken immediately to a hospital and operated on for hematuria. Wilms' tumor of the kidney was found. Such incidents show that a rare tumor and a peculiar accident may coincide.

All these considerations justify the attitude of medicolegal experts who refuse to regard a history of previous trauma as an adequate explanation of a given tumor, who insist on subjecting the evidence to close scrutiny, and who attach superior weight to the presence of other well known and adequate causes. Accordingly, several definite criteria have been widely recognized as essential for the acceptance of a traumatic origin of a tumor.

ESSENTIAL CRITERIA

1. Authenticity and Adequacy of the Trauma.—That an injury occurred is generally accepted by the courts on the statement of the patient, but for strictly scientific purposes such evidence must be regarded as inadequate for the reasons previously explained. The statement of the patient must be corroborated by eye-witnesses or, better, by circumstantial evidence such as the immediate discovery of signs of injury by an intelligent layman or physician. In many instances only the results of competent medical examination are worthy of credence. In the absence of such corroboration a careful investigation should be made of the circumstances of the injury, the terrain, the objects alleged to have been concerned, the exact sequence of events and the question whether the incidents described could have occurred or resulted in the alleged injury. Many a case falls down when a simple orderly inquiry of this sort is pursued.

The exclusion of previous injuries of the same sort is necessary; otherwise the antecedent conditions amount to chronic irritation and not a trauma in the strict sense. Shop-women frequently bump their breasts in pulling out bolts of goods. Hod-carriers constantly bruise their shoulders by the weight of the hod. Many persons repeatedly strike a shin, hip or shoulder against projecting objects to which they are daily exposed. Machine operators frequently strain or bruise certain tissues which are especially exposed in their particular occupations. Tumors that arise under such circumstances are more properly regarded as occupational diseases than as traumatic tumors.

The trauma must be adequate to produce some alteration in the structure of the tissue, and the least effect it can give is the rupture of small blood vessels, with hemorrhage and discoloration of the skin. It should also be capable of exciting some regenerative process; otherwise it is difficult to conceive how it can excite excessive and abnormal proliferation of cells.

Much importance attaches to the character of the wound and to that of the instrument causing it. Clean surgical incisions never lead to cancer. The retention of a blood clot or of fragments of necrosing tissue provides conditions in which abnormal reactions conceivably may occur. When foreign bodies or irritating chemicals, such as acids, tar and wood, are carried into a wound, healing is delayed, and atypical results may be expected. There are many reports of cancers of the skin following wounds of this character. No doubt many of these instances represent coincidence, while in others the tumor represents the combined result of injury and previous alteration of the skin. In all such cases one should inquire whether the patient has been exposed to tar or other petroleum product, or has had a course of arsenic therapy, or suffers from multiple keratoses.

2. Previous Integrity of the Wounded Part.—While courts and juries may accept the patient's statement that the injured tissue was previously entirely normal, the positive demonstration that a tumor is of traumatic origin requires proof rather than assumption. Most patients who acquire cancer assert rightly that they had been in excellent health. The majority of patients with cancer connect the beginning of the trouble with a trivial incident, the most satisfying one being an injury. Very often the occurrence of an injury, mild or temporarily disabling, combined with the recognition of a serious disease and with visits to the doctor, interrupts the patient's routine and enables him to state truthfully that he was well before the accident and continuously sick thereafter. Usually the only proof of the previous integrity of the site is the evidence of a competent medical examination. Adherence to this criterion would exclude many of the cases of supposedly traumatic cancer.

The incidence of cancer is sufficiently high to justify the pathologist in conceiving of normal tissue not as normal but as harboring a great variety of structural abnormalities, tissue rests, precancerous lesions and even miniature cancers. Moore found that in 16 per cent of persons between 20 and 90 years of age and in 29 per cent of those between 45 and 90 years the prostate shows miniature cancers. Marked cystic disease in one breast raises a presumption that cancer in the other breast arose on a basis of cystic disease. Many a case of supposed traumatic sarcoma of bone is rejected when a roentgenogram taken immediately shows that a tumor was well established at the time of the injury. The number of cases of multiple small tumors in elderly subjects seems to increase in direct proportion to the industry of the pathologist in searching for them. So strong is the evidence against the purely traumatic origin of most cancers that one must assume the attitude that a malignant growth claimed to be traumatic arises not in normal but in previously altered tissues. Traumas reveal more malignant tumors than they cause.

Traumatic Determinations: The presence of an unsuspected tumor tends to bring about the occurrence of injuries at the tumor-bearing area and to intensify the subjective symptoms and local effects of the injuries. The principle may be designated as traumatic determinism:

A man is found at the bottom of a stairs unconscious and with a hematoma of the scalp. He recovers but complains of headache and attacks of vertigo. After three months, the symptoms persisting, an operation is performed, which discloses exactly beneath the hematoma a slowly growing glioma of the brain. It is then disclosed that he had suffered from attacks of vertigo for some months before the accident. In one of these he became unconscious and fell down stairs.

A carpenter slid down a ladder and bruised his shin. The pain continued, and two weeks later a roentgenogram showed a sclerosing osteogenic sarcoma occupying the upper end of the tibia. The leg was immediately amputated, but pulmonary metastases had occurred, and these proved fatal. It was then attested that he had been noticed to limp and spare the limb for some weeks before the accident. It became evident that the tumor antedated the accident and interfered with the normal mobility of the knee joint.

A young woman fell down the steps of a subway and injured her kneecap. She continued working as usual for two months; then pain set in, and she was treated for traumatic arthritis for two months. At that time roentgenograms disclosed a large tumor of the lower end of the femur, many small cysts in the patella, several cysts in the upper ends of both femurs, the pubes and the lumbar vertebrae and pronounced scoliosis of the dorsal spine. The leg was amputated, and a benign giant cell tumor occupying much of both condyles was found. The structure was fibrous and therefore of slow growth. The tumor of the femur antedated the accident, and the general signs of fibrous cystic osteitis showed that she was suffering from Recklinghausen's disease complicated with giant cell tumor. The marked disease in both the patella and the femurs satisfactorily accounts for the accident which occurred without other explanation.

Cancer of the breast, tumors of the testis, cancer of the sigmoid, neurofibromas of superficial nerve trunks and many other tumors produce local conditions that include increased bulk, fixation in the organ, adherence to the skin and deep structures and often some inflammatory reaction. All these conditions tend to convert many simple blows, pressures, stretchings and like disturbances into forces capable of injuring the tissues, with pain and hemorrhage following, whereas in normal tissues the effects would have been nil. It is usually in this manner that injury brings to light an unsuspected tumor. Whenever an apparently trivial injury is said to have produced some peculiar and exaggerated effect, and a tumor is later discovered, it should raise the suspicion that the tumor antedated the injury.

3. Origin of Tumor at Exact Point of Injury.—Any reasonable theory of the traumatic origin of a tumor must assume that the tumor develops in tissues altered in structure by the trauma and not by some mild transmitted force leading to intangible nutritional disturbances of which one knows nothing. Such alteration in structure can be produced only at the exact point of injury or within narrow limits. A blow on the knee cannot be assumed to be connected with a tumor arising in the hip, and an injury of the nipple cannot be responsible for a cancer arising in the upper outer quadrant of the breast. Lesions limited to the skin do not necessarily affect tissues deep beneath the skin.

On the other hand, there may be severe injury to deep organs without obvious damage to the skin, but the extent to which such deep effects may be expected depends on many circumstances and becomes a matter of careful clinical judgment. In injuries of the skull the principle of contrecoup is of importance but difficult to evaluate. I have not found evidence that injuries of the cranium have been connected with epithelial tumors of the sinuses or the nares.

A serious injury may be produced in an abdominal organ, such as a rupture of the liver, spleen or stomach, without obvious damage to the skin. This result may be referred to the mobility of the abdominal skin and to the fixation of the liver and spleen. Much less frequently a movable organ like the stomach or the intestine may be injured without obvious injury to the skin. When both the skin and the deeper injured tissue are fixed, the assumption that the deep tissue alone may be damaged must be regarded with much caution.

When the body falls from a considerable height and is subjected to general mechanical violence, the way is open for the assumption that a tumor in any organ may result, but unless there are definite symptoms pointing to injury of the organ involved in tumor there is no ground for assuming that its condition is due to the accident. It is difficult to conceive how a general concussion of the body can give rise to a malignant tumor at a particular point in which no structural damage can be demonstrated.

4. Reasonable Time Limit Between Injury and Appearance of Tumor.—It is difficult to establish any definite limits of time within which a tumor may reasonably be ascribed to a trauma. Presumably the malignant process may represent a part of the original but generally somewhat delayed healing reaction, and thus appear within a few weeks. With very rare exceptions there is an interval of from three to four weeks or more before there is any definite sign of malignant growth. According to Sauerbruch the interval for sarcoma should not be under three weeks, while for carcinoma it may be as long as ten or twenty years. The absence of such an interval strongly indicates that the tumor antedated the injury. In some of the cases acute traumatic bone sarcoma appears very soon after the injury, but nearly always after a certain interval. I have seen several cases regarded as examples of sarcoma occurring within two weeks after injury which proved to be instances of myositis ossificans or benign exuberant callus. The histologic structure of tissues injured in football games is notoriously difficult to distinguish from that of sarcoma, and many limbs have been unnecessarily amputated for this reason.

The type of the tumor often decides whether it could have developed in the particular period of time. Again, the malignant process may be presumed to have resulted late, months or years, after the injury, from the disturbance caused by scarring and interference with function and nutrition. Yet the passage of time allows the entrance of many other factors into the causation, so that the longer the interval the less certainly may the tumor be referred to the trauma. Here again the type of the tumor is often of decisive importance.

Continuity of Symptoms: The so-called bridging symptoms between the injury and the appearance of the tumor are of interest and occasionally of importance. When the evidence shows that a wound of an apparently normal tissue never healed and that pain, swelling and discharge persisted for weeks until the appearance of a definitely malignant process, one must accept a presumption in favor of the traumatic origin and rely on other features if the traumatic theory is to be rejected. Yet, when dealing with tumors of the internal organs, I have not found that bridging symptoms are of great significance, because it is well known that the first symptoms of cancer of the stomach, lung and other organs frequently appear suddenly and that they are invariably referred by the patient to some incident, often trivial, and almost always to an injury if trauma of any sort has occurred within the memory of the patient. These considerations apply also to the question of aggravation. Several German authors have pointed out the unreliability of bridging symptoms. When an unsuspected tumor is injured, the symptoms are apt to be out of proportion to the injury and are apt to continue until the presence of the tumor is recognized, whereas when normal tissues are injured,

they generally heal normally, and a symptomless interval separates the injury from the signs of tumor.

5. Positive Diagnosis of Presence and Nature of Tumor.—The need for this criterion will be obvious to all who are familiar with the uncertainties of the clinical diagnosis of tumors. Troell [3] reviewed 105 cases registered as instances of bone sarcoma in the hospitals of Stockholm and found that 1 in 4 was not a case of sarcoma. The complete modern diagnosis of structure, grade of malignancy, origin and probable course of a malignant tumor furnishes information essential in medicolegal interpretations. Biopsy and autopsy should therefore be made mandatory. Microscopic examination often reveals that what has been supposed to be a primary tumor is tuberculosis, syphilis, lymphogranuloma or some form of metastatic carcinoma. It may show that the tumor is a slowly growing process the genesis of which antedated the injury. Histogenetic diagnosis should replace the simple histologic report, for there is a wide difference in the medicolegal relations between spindle cell osteogenic sarcoma and neurogenic sarcoma, between lymphosarcoma, lympho-epithelioma and round cell carcinoma and between many other varieties of tumors, but these important distinctions are seldom recognized in current medicolegal reports.

The tumor must be of a type which can reasonably be referred to a trauma and which is consistent with all the facts in the case. Judgments in this field must be based on a broad knowledge of the causes, natural history and structural features of the different forms of tumors.

To be the result of an injury a tumor must be of a type which can be referred to disordered processes of regeneration in the injured tissue. One cannot refer a cancer in bone to a bone injury, because there is no possible source of such a tumor in bone. Yet adamantinoma of the tibia has sometimes been traced to the traumatic transfer of a fragment of epidermis and epidermal glands into the underlying bone.

The traumatic theory is applied with difficulty to the entire group of tumors arising from tissue rests. Evidence has never been adduced to show that such a rest had been incited to growth by local injury, although Ribbert was willing to consider such a possibility. Accordingly, one must exclude from the field of traumas such tumors as adrenal-rest and other peculiar tumors of the kidney, mixed tumors of the salivary glands in various locations, branchiogenic carcinoma of the neck, uterine myoma, aberrant thyroid tumors, myoma and myosarcoma of the gastrointestinal tract and the entire group of complex tumors of the cephalic and caudal extremities of children.

Likewise local teratoids and mixed tumors, such as fibro-adenoma of the breast and its variants, carcinoids of the appendix, adamantinomas

3. Troell, A.: Virchows Arch. f. path. Anat. **283**:550, 1932.

of the jaw and many complex neurogenic tumors, must be excluded from the traumatic class. A highly embryonal cellular character is difficult to reconcile with an origin from trauma, and such a growth can reasonably be referred only to the embryonal character of the cells of origin.

A review of reports in several languages of tumors alleged to be traumatic leaves the impression that legal medicine is struggling along in many countries with very meager aid from exact pathology. Industrial surgeons and most pathologists are not much concerned with the relation between tumor structure, histogenesis, rate of growth and possible behavior of neoplasms. Many cases, obscure in all other respects, could be readily resolved by reference to this source of decisive information.

Thus, two well known authors, in an otherwise astute contribution, reported some of their cases as instances of "sarcoma" and "carcinoma." They asked one to believe that an epidermoid carcinoma can arise and destroy the whole body of the mandible for 2 inches (5 cm.) and extensively invade the cervical nodes in three and one-half months.

AGGRAVATION

The theory that an aggravation of an existing tumor may occur through trauma has assumed much importance in compensation courts. The law granting an award for an aggravation of a tumor seems reasonable when the progress of the disease and its fatal termination are definitely hastened, or when trauma introduces into the course of the malady features and complications which do not normally belong to the disease and which are injurious to the well-being of the patient. It can hardly be assumed that the law was intended to insure workers against the occurrence and natural course of malignant tumors that arise from causes not connected with industry.

One must consider first what constitutes an aggravation. An injury which hastens the death of the patient must be accepted as an aggravation. Such a result is seen when a trauma causes immediate hemorrhage, infection and collapse in an advanced case of cancer of the stomach or other internal organ, or when a fracture is precipitated in a bone which is the seat of a sarcoma, with subsequent severe hemorrhage and infection. When, however, the trauma merely leads somewhat prematurely to complications which are inevitable in the course of the disease and which are about to occur in the normal course, it seems inequitable to assume that any aggravation has occurred. The normal course of the malady has not thereby been altered. The small hemorrhages of gastric and other internal cancers, the initial attacks of pain in sarcoma, the erosion of superficial ulcers, the infarction of bulky tumor masses, the sloughing of infected tumors, the sudden closure of

hollow viscera and many other events are natural features in the course of the disease, are often the initial symptoms of the disease and cannot be regarded as aggravations. All these incidents are bound to occur though the patient remains in the ordinary environment, and they frequently appear when he is lying in bed, walking up stairs, straining at stool or suffering from bad news. Unless the trauma introduces into the course of the disease something which does not belong there and which works to the disadvantage of the patient, aggravation may not properly be assumed.

Trauma may cause temporary complications the effects of which disappear in due time and have no permanent influence on the total course of the disease. Thus, a patient with unsuspected carcinoma of the lung falls into a ditch and breaks his arm, which heals after six weeks. A year later he dies from the pulmonary carcinoma, which has run an average course. He should receive compensation for the fracture but not for the carcinoma. A woman with generalized carcinoma of the breast with metastases in many bones is shaken up in a collision of a public conveyance and has to remain in bed for a month, after which the malignant disease runs its natural course. Here there is no definite ground for assuming aggravation of the cancer.

When injury discloses a tumor and leads to earlier operation, which may be the best method of treatment, the chances of recovery are improved, and aggravation may not be assumed.

It is generally assumed that trauma may activate a latent cancer and increase the growth energy of the cells, but the grounds for this view are unsatisfactory. It is doubtful if any primary cancer is ever in a state of quiescence, although the early growth may be slow. The idea that trauma may endow the cells with greater powers of growth must be rejected. The growth energy of tumor cells is determined by the conditions of origin, although its manifestation may vary with the environment.

Lubarsch [4] bruised mammary fibro-adenomas in rats and epitheliomas in dogs by repeated blows of a hammer and by crushing them with forceps, but failed to find any increase in growth or in the number of mitoses. In some mice with 2 tumors each the one traumatized regressed or remained stationary, while the other grew. As a rule he found that any marked disturbance of circulation was followed by regression.

Marsh [5] subjected malignant tumors in mice to various severe injuries and found retardation as often as acceleration of growth. When a large tumor was traumatized, infection and sloughing sometimes followed, with the earlier death of the animal, but with a smaller tumor retardation was rather more prominent than any sign of acceleration.

4. Lubarsch: Med. Klin. **8**:1651, 1912.
5. Marsh, N. C.: Am. J. Cancer **17**:735, 1933.

There are several conditions in which severe trauma must be accepted as capable of accelerating growth and hastening death: 1. When an encapsulated tumor suffers rupture of the capsule, pressure is relieved, and the tumor may grow more rapidly for a time. Whether the injury thereby hastens the total course of the disease must be judged by the general clinical picture. 2. When trauma introduces infection, especially in a superficial tumor, the course of the disease may be hastened owing to more active proliferation of tumor cells and probably, in some cases, to metastases which have been favored, but whether such results have actually occurred must be determined by clinical judgment, by one who is familiar with the natural course of the disease. One not infrequently sees an increased number of mitoses in cells surrounding pus foci in epidermoid carcinoma. 3. In several thousand diagnostic punctures by needle and trocar, I have not seen any evidence of increased local growth or metastasis. Surgeons have not been deterred from the universal practice of taking specimens for biopsies, often by resections of considerable size, because of any observed increase in the growth of the tumors or danger of metastases.

Wood [6] performed many biopsies on transplanted carcinomas of mice without observing any increase in growth. Rohdenburg [7] collected a long series of cases in which partial removal of a tumor was followed by regression of the remainder. On the other hand curettage or partial removal of a bone sarcoma is very apt to be followed by prompt recurrence and more rapid growth and sometimes by a definite change in the structure of the tumor, but insults on such a scale rarely occur by accident. Accordingly, one must conclude that unless a tumor has received a severe crushing injury there is no definite danger of increased growth or of metastases.

In general, opinions regarding aggravation must be based on broad clinical judgment and on observation of facts, rather than on the pursuit of speculative possibilities.

CAN TRAUMA CAUSE APPEARANCE OR LOCALIZATION OF METASTASES?

It is surprising how many metastatic tumors are referred by the patients to previous injuries. This occurs often enough to suggest that injuries are in some way responsible for metastases. It is well known that the lowered resistance and obstructed circulation of traumatized tissue may gather bacteria from the blood stream and lead to local abscesses. Burrows,[8] in an elaborate investigation, pointed out many

6. Wood, F. C.: J. A. M. A. **73**:706, 1919.

7. Rohdenburg, G. L.: J. Cancer Research **3**:193, 1918.

8. Burrows, H.: Some Factors in the Localization of Disease in the Body, London, Ballière, Tindall & Cox, 1932.

interesting features of the localizing effects of injured and especially infected tissues, but he was unable to find any definite application of this doctrine in the field of cancer. Lubarsch [4] failed entirely to localize metastases in tumor-bearing mice by fracturing bones.

Jones and Rous [9] placed kieselguhr, dead tumor cells and glass rods in the peritoneum in many mice and found much greater tendency of injected tumor cells to become implanted in the regenerating tissue about the foreign material. Since in tissue cultures regenerating fibroblasts are more active than resting fibroblasts the investigators concluded that the regenerating tissue was more apt to provide the stroma necessary for the implantation. However, implantations were not infrequent in the control animals, and it is not clear that the conditions in the peritoneum are comparable to those of injured human tissues. The evidence drawn from many experiments with chicken sarcomas, reviewed by Foulds,[10] shows that tumor cells may be localized by various types of injury, but also by almost any structural abnormality in the tissues.

It may be conceived that the damaged capillaries in a traumatized area may sift out vagrant tumor cells, which are able to grow in the devitalized area as do bacteria, and thus that a metastasis may develop which might not otherwise appear. In order that any such event should occur it is necessary that tumor cell emboli should frequently be present in the circulation. Such a condition exists only in the advanced stages of malignant tumors. The chances are overwhelmingly against a single or an occasional or a precocious embolus lodging in a traumatized focus. The assumption that tumor cells are constantly being discharged into the circulation is not supported by definite evidence. Tumors probably vary in this respect, and it is possible that some very malignant cellular growths release numerous cell groups even in their early stages. These cells must be sifted out by the lungs. Schmidt found some indications that tumor cell emboli may be destroyed in the lungs. If by some rare chance vagrant cells do lodge in such a traumatized area, there is some reason to conclude that the conditions for growth are somewhat better there than in the lung or the bone marrow, where metastases usually appear. I believe, therefore, that the possibility of the localization of a metastasis by a trauma may not be excluded. However, a trauma at a distance cannot have dislodged the vagrant cells; the influence of a trauma is limited to a particular localization of tumor cells which would probably produce a metastatic tumor somewhere in the body. Accordingly, one must conclude that if a trauma causes a localization of

9. Jones, F. S., and Rous, P.: J. Exper. Med. **20**:404, 1914.

10. Foulds, L.: Scient. Rep. Invest. Imp. Cancer Research Fund (supp.) **11**:1, 1934.

tumor cells with metastasis, this event occurs only in the late stages of the disease; that is, at a period when the metastatic tumor cannot be regarded as influencing the course of the disease. Experience confirms the validity of the principles stated:

A laborer who claimed to be in good health fell into a ditch and fractured a humerus. The fracture healed slowly, and after four months a rapidly growing tumor appeared about the callus, and other tumors appeared in the skin of the chest, in the axilla and finally in the lungs. A diagnosis of traumatic osteogenic sarcoma was made, but after a year the body was exhumed and a large carcinoma of the lung was disclosed with metastases in many organs and particularly in the subcutaneous tissues of the chest.

A woman struck her head against a closet door, and a few weeks later a persistent swelling appeared in the pericranium and grew rapidly. Aspiration revealed a malignant adenocarcinoma. It then was found that she had had an operation for a carcinoma of the thyroid gland two years previously.

A workman struck his head against a boat hook, sustaining a mild bruise without bleeding. No attention was paid to the incident. Some weeks later a rapidly growing tumor appeared, which proved to be a malignant adenocarcinoma. General roentgenographic examination disclosed a tumor of a kidney and many metastases in the ribs and pelvis.

A carpenter stated that he had bruised his chest against an alarm clock, but without any laceration or ecchymosis. A few weeks later a rapidly growing adenocarcinoma fungated through the bone and skin. Examination disclosed a large tumor of the kidney with many metastases in the lungs and in the skeleton. In all these cases the metastatic tumor in question probably existed before the injury, and only in the case of the fracture was the injury an authentic or adequate factor in the localization of the metastasis.

The following case suggests the localization of a metastasis in tissues receiving hypodermic injections. In June 1933, a physician came to the Memorial Hospital for the Treatment of Cancer and Allied Diseases with an embryonal carcinoma of the testis and epigastric metastases. The abdominal mass disappeared under irradiation. In October roentgenograms showed pulmonary metastases, which also disappeared under irradiation. In November the patient experienced severe headache and hemiplegia, and he was given several hypodermic injections in the deltoid region. Under irradiation he recovered from the hemiplegia and was able to return to his home. In December he died in the course of another cerebral attack. Two weeks after the injections a nodular swelling had developed in the subcutaneous tissue in the area of the injections. Autopsy disclosed tumor masses with the structure of the testicular growth only in the brain and in the deltoid region.

TRAUMA AS A PERCIPITATING FACTOR IN CAUSATION OF CANCER

The great rarity of authentic cases of traumatic cancer, the uniform failure to produce the disease experimentally by simple trauma and the highly specific nature of known cancerigenic agents have led pathologists to conclude that a single trauma is itself incapable of producing a malignant tumor, and that it must always act in combination with equally or more important factors. What are these associated factors?

In mice rendered highly susceptible by selective breeding Syle noted the frequent incidence of cancer after trauma, but no such conditions of susceptibility exist in man.

The incidence of tumors of the breast, nerve trunks and bones reveals a certain hereditary tendency. While theoretically an exalted state of hereditary predisposition may render these organs more susceptible to the traumatic development of cancer and sarcoma, I have never been able to detect any such influence in medicolegal cases. In chicken sarcoma the exciting or growth agent unites by a special affinity with muscle tissue (Murphy), and when the muscle is traumatized a tumor develops at the injured point. But in human pathology there is no known parallel with chicken sarcoma. When the heavily tarred skin of rabbits is scarified, multiple tumor nodules may appear after a variable interval in the scarified lines. Apparently the trauma precipitates the development of cancers, in tissues which are on the point of yielding them spontaneously.

To a considerable extent the application of this doctrine is exemplified in the human subject, since it is well known that injuries of many kinds, especially if repeated, cause the appearance of cancer in roentgen ray dermatitis, in scars of heat burns and in simple chronic ulcers. It seems reasonable to conclude that in this field one finds the explanation of many apparently traumatic cancers which arise in tissues long prepared by some previous injury or irritation, with or without recognizable precancerous changes. In the case of cancer of the bladder due to aniline the exposure may have occurred many years before. Since in all such conditions the occurrence of cancer is frequent, the question arises whether the cancer is the result chiefly of the injury or is merely the natural expression of the original disease. The decision becomes a matter of careful clinical judgment, and in certain cases the trauma will be accepted as the precipitating cause. Such conditions call for recognition by the courts of a form of partial liability.

It is widely assumed that traumas may hasten the progress of various precancerous lesions, such as chronic mastitis, keratoses and benign tumors. The assumption is possibly correct, but the fact that trauma produced such a change in any given case must be established by clinical evidence, and the actuality is extremely difficult to prove. The natural tendency of such lesions is toward cancer, and clinical observation shows that in the vast majority of cases of injuries to tissues with precancerous lesions the tissues heal as do normal tissues, while in some cases the injuries actually interfere with the further progress of the lesions.

One occasionally notes, especially in German literature, the policy of assuming that while a trauma has not originated the cancer it has acted on a slumbering tumor anlage and caused it to become an active

carcinoma. This policy avails itself of several unwarranted assumptions: 1. What is the tumor anlage? If it is a precancerous lesion or a tissue rest there can be no evidence that it existed at the injured point. 2. If such an abnormality did exist, one has no evidence that trauma caused it to change its course and become cancerous. 3. If the anlage is a miniature cancer, there can be no proof that it existed or that the trauma accelerated the growth. On the contrary, the observations of Lubarsch and Marsh show that even with an established cancer trauma is just as likely to interfere with the growth as to accelerate it. In all such cases it is impossible to establish a reasonable probability by a series of assumptions, and it is far more reasonable to look for the ordinary known causes of the cancer.

CONSIDERATION OF SPECIAL TYPES OF TUMORS

Neurofibroma.—Neurofibroma is a manifestation of Recklinghausen's disease. This remarkable dyscrasia, in all its phases, may be traced back to a hereditary and congenital disturbance in the fetal ectoderm affecting mainly the skin and nervous system. When one reviews the various disorders attributable to neurofibromatosis, notes the occasional occurrence of tumors and observes how uniformly the tumors are associated with other features of the dyscrasia, the conclusion must be reached that a trauma can play a very minor part, if any, and that the course of the malady is determined by intrinsic factors.

Studies covering a vast number of experiments in cutting, suturing and transplanting nerves reveal a very moderate regenerative capacity, always self-limited in nerve tissue.

Clinical experience reviews the innumerable lacerations, fractures, amputations, nerve sutures and infections to which nerves are exposed and can point only to the low grade amputation neuroma as evidence of a neoplastic tendency.

Dupuytren's contraction, or rider's hand, is a neurofibroma, but results from repeated blows and stretching. Desmoid tumors probably include a neural element, but here again continued stretching enters. The literature contains few references to traumatic neurofibroma. In several cases in which the patient attributed the tumor to an injury, I have been unable to substantiate the claim, but occasionally the history in such cases is difficult to analyze. The fact that neurosarcoma recurs repeatedly after operations (in one case, 21 times), while retaining the original structure unchanged, renders aggravation extremely improbable. Rather frequently injury brings to light an unsuspected neurofibroma.

Lipoma and Liposarcoma.—According to Toldt, fat tissue develops from isolated embryonal fat anlagen or organs, each with an independent

system of blood vessels, in the meshes of which the fat tissue forms by infiltration of perivascular cells. The common lipoma illustrates this mode of origin by producing a multilobed tumor mass which is so isolated from the surrounding fat tissue as to suggest a separate blood supply. It is difficult to conceive how trauma can provide such a separate set of blood vessels. All that trauma may do is to disarrange the preexisting blood vessels and allow the growth of separate, individual fat cells. These effects are constantly seen in the regeneration of injured fat tissue with the production of oil cysts and the proliferation of fat cells about them and foreign body giant cells, yielding the picture of traumatic fat necrosis.

The spontaneous appearance, multiplicity, symmetrical distribution, frequent admixture with angioma and neuroma and striking association with hereditary neurofibromatosis compel one to assign the origin of lipoma to congenital or acquired disturbances of structure of the affected tissues and to nutritional abnormalities.

Nevertheless, the literature contains many references to lipomas alleged to be traumatic, in a few of which the sequence of events is suggestive of such an origin. Wolff [11] reported 1 case following a single trauma, and added 3 others that were referred to multiple injuries about the shoulder. Lieschke's [12] collection of 81 cases includes miscellaneous clinical material, and there is no evidence of any special effort to scrutinize the facts. With the same facility Bosse and Lieschke [13] referred several cases of scrotal lipoma to contusions. On the other hand, among 28 cases alleged to be traumatic Wurz found only 1 case in which such an origin could be considered. Stern [14] considered the general pathology and clinical features of lipoma and rejected the traumatic theory entirely.

That repeated traumas may induce the growth of certain peculiar types of lipoma such as lipoma arborescens of the knee joint or lipomas about old inguinal and ventral hernias is suggested by more direct and more acceptable evidence. The rupture of joint capsules or intermuscular fasciae may allow a hernial protrusion of fat lobules in which repeated impacts, venous congestion and gradual traction may induce a neoplastic growth of low grade. It is probably through such indirect effects that lipomas which are actually attributable to trauma must be explained.

Since fat tissue may react to injury by active proliferation of fat cells, the basis is laid for the development of liposarcoma after trauma. Clinical experience indicates that in rare cases crushing injuries involving fat tissue may result in certain forms of liposarcoma. In these cases

11. Wolff, S.: Zur Entstehung von Geschwülsten nach traumatischen Einwirkungen, Inaug. Dissert., Berlin, 1874.

12. Lieschke, M.: Lipom und Traum, Inaug. Dissert., Berlin, E. Ebering, 1911.

13. Bosse and Lieschke: Therap. Rundschau **3**:433, 1909.

14. Stern, R.: Ueber traumatische Entstehung innerer Krankheiten, ed. 3, Jena, Gustav Fischer, 1931.

the previous integrity of the tissue may be reasonably assumed, the adequacy of the trauma is attested by its severity, and the continuity of symptoms connects the tumor directly with the damage of the tissue, so that little ground may remain for rejecting the traumatic theory of origin:

> An intelligent woman stated that she was in the habit of striking her thigh against a projecting bureau while passing through her apartment. After some weeks a persistent lump formed at that joint, and after successive blows the lump enlarged to the size of an egg. In the sixth month it was excised, and the tissue showed an active diffuse growth of atypical fat cells with distinctly sarcomatous features.

In my experience it is the adult type of liposarcoma with opaque granular spindle-shaped and polyhedral cells which seems to follow trauma. The embryonal type of myxoliposarcoma or pure myxosarcoma, commonly occurring in the groin, is of embryonal origin; in my material no such growth has been preceded by trauma.

Bone Tumors.—The reactions of bone tissue to injury, fracture and other severe traumas give evidence favorable to the theory that severe traumas may be the essential cause of certain benign and malignant tumors of bone.

Starting with this broad assumption, one must next determine what are the reactions to injury which suggest a relation to sarcoma and what are the types of bone sarcoma which may possibly be referred to traumas.

After fracture, especially when the part is imperfectly immobilized, there may be excessive callus formation yielding a tumor-like swelling clinically resembling sarcoma. In a case of fracture of the clavicle, a tumor mass 5 cm. in diameter formed in eighteen days and was resected as sarcoma. It showed very active growth of practically normal bone arising chiefly from muscle tissue and some islands of atypical cartilaginous callus. In myositis ossificans the reactions are usually those of excessive production of normal bone with much atypical cartilage. Yet in some cases the reaction may result in a very cellular tissue resembling sarcoma with atypical bone and very atypical cartilage such as are seen in some osteogenic sarcomas. It is a notorious fact that many limbs have been amputated for sarcoma because the tissue strongly resembled osteogenic sarcoma. In 2 cases of injury in a football game the tissue removed four weeks later was passed as sarcoma by five pathologists in different parts of this country, but the condition ran the usual favorable course of myositis ossificans. It is thus apparent that the reactions of bone to injury often approach the character of osteogenic sarcoma, especially those types which form bone and cartilage. What factors turn the balance into true malignant sarcoma are not known.

That some entirely new factors, not connected essentially with the injury, enter into the case when a true sarcoma results is strongly indicated by the vast number of fractures, operations on bone, bone grafts and other injuries of bone which are never marked by the development of sarcoma. Special injury to blood vessels or muscles may be excluded, because the sarcomas that apparently are traumatic do not usually involve muscles or produce extensive hematomas. One is thus forced to resort to the theory that a local predisposition is at work, about which nothing definite can be said.

A more substantial explanation is that there has been a preexisting silent tumor focus which the injury brings to light. Roentgenograms immediately taken have often disclosed the presence of a preexisting tumor. If the practice of taking roentgenograms immediately after injuries to bone were universal, the majority of the allegations that trauma caused bone sarcoma would, I believe, be eliminated.

In the general etiology of bone sarcoma there are many facts which tell against the traumatic theory. The disease belongs to young subjects or young adults, indicating that it is due to some disturbance of growth resulting from intrinsic factors. Chondromas are often multiple and often hereditary, and occasionally osteogenic sarcoma appears in several bones. Bone changes are common in scurvy and rickets, and those in rickets are certainly connected with some of the medullary chondrosarcomas and osteosarcomas. There are many other forms of nutritional disturbance in bone which may well form the basis of tumors. In about 8 per cent of cases of Paget's disease in adults osteosarcoma (Codman) develops, and nearly all osteosarcomas in elderly adults arise on this basis. Fibrous osteitis is common in young subjects, and it may well be regarded as a probable basis for sarcoma in early periods of life. In many cases of osteogenic sarcoma the bone marrow shows changes of the same general type as in fibrous osteitis. There have been some reports of traumatic osteitis fibrosa cystica, but this disease must now be attributed mainly to disturbances in calcium metabolism.

Infection probably plays a definite rôle in some cases. Primary abnormalities in the blood vessels are probably related to the telangiectatic types of bone tumors. Clinical experience shows that the great majority of osteogenic sarcomas arise without any traumatic implication, and that in the vast majority of injuries of bone the tissues heal normally. Therefore, when a sarcoma of bone follows a trauma there is a strong presumption that the disease is not caused by the trauma but results from one or more of the aforementioned conditions which are positively known to produce it.

What types of malignant bone tumors may be considered as possibly traumatic? The character of the reaction of bone tissue to injury indicates that only the bone formers and their variants may safely be referred to traumas. A typical exuberant cartilaginous callus and atypical

bone trabeculae are prominent in this reaction, and these elements belong chiefly to that group designated by the American Registry as medullary and subperiosteal sarcoma. Formerly this group was termed simply "periosteal sarcoma," but it has now been subdivided.

The bone-forming tumors are composed of large polyhedral and large spindle-shaped cells, occasionally mononuclear tumor giant cells and much or little atypical, poorly formed cartilage and bone. The recognition of the possible variants of this group is the task of an experienced tumor pathologist.

The true periosteal sarcomas are composed of small spindle-shaped cells and seldom or never contain any trace of bone or callus. They presumably arise from the outer layers of the periosteum. In my experience the few osteogenic sarcomas which seemed probably of traumatic origin have been of the bone-forming type:

A boy of 18 years carrying a heavy sack of mail over freshly broken stone fell and suffered a contused and lacerated wound over the middle two thirds of the tibia with some bleeding. The limb remained painful for two months; swelling was noted in the third month, and a roentgenogram taken after the fourth month revealed irregular nodular thickenings over the injured area. In the amputated limb the anterior portion of the shaft of the tibia, over a segment 6 inches (15.2 cm.) long, was the seat of a cellular sarcoma with much atypical cartilaginous callus and poorly formed bone.

A boy of 14 years received a severe blow above the inner femoral condyle while playing basket ball. There were severe pain, immediate swelling and discoloration of the skin. He was helped home and put to bed. After two weeks the swelling had partly subsided but thereafter remained stationary, and after the fourth week slowly increased. In the eighth week a roentgenogram disclosed a destructive process affecting 2 inches (5 cm.) of the shaft and contiguous medulla with a painful tumor of the soft parts. Roentgen therapy produced only slight, temporary relief, and the leg was amputated in the fourth month. Death followed from pulmonary metastases. The tumor was an extremely vascular and cellular subperiosteal and medullary bone-forming sarcoma.

To what extent the acceptable traumatic bone sarcomas recorded in the literature follow this type cannot be determined, because the structural type is not usually reported. At present my cases are too few to permit the assertion that all traumatic bone sarcomas are necessarily of the bone-forming type. Sebestyen [15] described 3 bone sarcomas which followed shortly after war injuries, all of which were bone formers.

The medullary osteosarcomas, chondrosarcomas and myxomas find their best explanation in congenital or acquired abnormalities of the structure of the involved bone. The tissue of origin of these tumors is well protected from injury. In cases of endothelioma of bone I am disposed to discount the occasional history of trauma because the structure indicates an origin from structural anomalies in the fine blood

15. Sebestyen, J.: Arch. f. klin. Chir. **136**:716, 1925.

vessels of bone and bone marrow. The subjects are usually of delicate constitution, and the vast majority of them give no history of injury. The various types of myeloma must be referred to infectious and nutritional disorders. Liposarcoma is a medullary tumor of obscure etiology.

The recent demonstration that giant cell tumors are essentially a phase of Recklinghausen's disease, osteitis fibrosa cystica, that this disease is often associated with tumors or functional disturbances in the parathyroid glands with excessive mobilization of calcium, that the disease may be cured by extirpation of the parathyroid tumor, and that it may be produced in its main features by administration of parathyroid extract leaves little basis for the traumatic theory of the origin of these common lesions (Barr, Barr and Bulger[16]; Jaffe and Bodansky[17]). In some cases the giant cell tumors have appeared in nearly every bone in the body. In many others they have appeared in one bone at one time and later in other bones. Efforts to produce giant cell tumors by inducing traumatic hemorrhage have failed. Teichmann[18] introduced magnesium needles into the marrow in dogs, producing cavities which, after the resorption of the magnesium, were filled with normal marrow tissue. He concluded that trauma alone is insufficient to produce bone cysts. A primary absorption of bone trabeculae by withdrawal of calcium associated with a peculiar and specific reactive process not seen after pure trauma seems to be the regular sequence of events in the origin of these tumors. If giant cell tumors result from traumas they should show definite evidence of organizing blood clot or of chronic inflammation of fat tissue, but these signs are generally missing in such tumors and when present seem to be secondary. In view of these considerations, any history pointing to the traumatic origin of a giant cell tumor must be scrutinized with the greatest care.

Chordoma.—Ardoin concluded a report of miscellaneous cases of tumors supposed to be traumatic by relating the observations in 4 cases of chordoma in which he was able to obtain a history of trauma. In his case 2 the trauma as described was adequate: The patient fell a distance of 2 meters (about 79 in.) striking on the sacrum. There were severe pain and urinary disturbance lasting two weeks. Ten months later painful micturition appeared, and a tumor gradually developed over the whole posterior surface of the sacrum. The nature of the traumas in the other cases is not clearly stated. It does not appear that the author paid due attention to the natural history, known conditions of origin and long latent period of chordoma. There were no

16. Barr, D. P.: Am. J. Cancer **16**:1424, 1932. Barr, D. P., and Bulger, H. A.: Am. J. M. Sc. **179**:449, 1930.

17. Jaffe, H. L., and Bodansky, A.: J. Exper. Med. **52**:669, 1930; Arch. Path. **11**:207, 1931.

18. Teichmann, T.: Arch. f. orthop. u. Unfall-Chir. **7**:6, 1929.

data on the previous condition of the patient. Stanton [19] reported 2 similar cases, in one of which the man sat down hard on the coccyx two years before, and in the other the patient remembered having received a blow on the head four years before.

Cancer of the Skin.—Cancer has often followed wounds of the skin, but with rare exceptions the connection between the trauma and the cancer is indirect. The wounds that are followed by cancer of the skin are nearly always complicated; the long interval of several years permits other factors to enter, so that it is difficult to determine whether the cancer is chiefly referable to the injury or mainly and essentially to the subsequent and complicating events.

Lacerated wounds which become infected and heal slowly may leave large scars in exposed situations which are subjected to unusual irritations. Under these circumstances cancer occasionally develops, usually after a long interval. The entrance of foreign bodies, such as fragments of wood, steel, earth and clothing delays healing and alters its course so that cancer may result. In rare instances this result is observed within a few months and without complete healing of the wound. The connection is then rather direct.

An injury of underlying bone followed by chronic osteomyelitis has in some cases been complicated by cancer of the skin, usually after a long interval. Repeated wounds, the one acting on the scar tissue of the other, appear to be the most common sequence of events in traumatic cancer of the skin. Wounds and infections of the scars of burns are well known to lead to cancer, but as a rule only if the scars are very old. Here the question arises whether the cancer is the result of the burn or is a wholly new process dependent on the predisposing condition in the scar.

Carnett [20] and Burton reported a case, often cited, of traumatic cancer of the skin in a boy of 22 years who received a lacerated wound of the forearm while playing baseball. The wound never healed, and extensive suppuration developed. The process was a very anaplastic carcinoma, not squamous, and the date of its appearance was not determined. The patient died of pneumonia one and one-half years after the discovery of the carcinoma. Here the injury, the suppuration and the various surgical procedures must be considered in determining the origin of the cancer.

Chemical burns, especially those by hot tar, not infrequently lead to cancer, and Gunsett [21] reported cases in which the cancer appeared within a few weeks after the burn. Schad [22] reported 2 cases of gunshot wound of the face in which squamous carcinoma developed in less than six months.

19. Stanton, O. L.: Canad. M. A. J. **27**:20, 1932.
20. Carnett, J. B.: S. Clin. North America **7**:243, 1927.
21. Gunsett, A.: Bull. Assoc. franç. p. l'étude du cancer **19**:459, 1930.
22. Schad, M.: Ztschr. f. Krebsforsch. **32**:43, 1930.

Haagensen [23] reported from the Memorial Hospital for the Treatment of Cancer and Allied Diseases many cases illustrating the conditions under which cancer of the skin may follow trauma. In most of these the circumstances were attested with fair but not absolute certainty:

> A fox bite on the back of the hand in 1922 was followed by normal healing, but in 1927 there were scabbing and ulceration, and in 1929 basal cell cancer appeared. A horse bite on the hand in 1901 left a scaly area which ulcerated in 1922 and then showed epithelioma. A dog bite in 1919 was cauterized but never healed, remaining crusted, and in 1923 squamous carcinoma appeared. In 3 cases splinters of steel or wood entered the wound, and cancer was found after seven weeks and one year. A severe wound from a crushing blow dealt with a hammer was found to show cancer after one year. A horse tramped on a man's great toe in 1914, leaving a chronic suppurating sore which in 1919 showed cancer.

The familiar traumatic epidermoid cyst results from the transfer of a fragment of epidermis into the derma or deeper tissues. It is generally benign but in many cases becomes malignant. A similar origin may be cited in most, if not all, of the cases of tibial adamantinoma appearing within a few months (Fischer [24]) or several years after an injury to the shin (Ryrie; [25] Holden and Gray [26]).

While there is no satisfactory evidence that normal scars are specially prone to cancer, it is clear that such scars are prone to subsequent injuries and to infection. A very long interval permits the entrance of many new accidents as well as the late action of arsenic or sunlight, which might be effective on normal skin. The wounded area may not be regarded as immune to subsequent cancer-producing agents. Therefore, the possibility that the late cancer is merely a coincidence must be considered. Since infection and delayed healing belong to complicated wounds, if healing is never complete and bridging symptoms persist and the cancer appears within a few weeks or months, the connection is more direct.

On reviewing the foregoing data it appears that cancer of the skin may be regarded as traumatic only when it develops before healing is complete. When the wound heals normally and remains healed for a substantial period any subsequent development of cancer must be attributed to subsequent events. Otherwise a man who sustained a wound of the skin would for the rest of his life enjoy insurance against all later cancer-producing hazards affecting that area. Some form of recognition of partial liability seems to be required in such cases.

Melanoma.—The dramatic incident of immediate local recurrence and metastases of apparently benign moles after surgical excision

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23. Haagensen, C. D.: Am. J. Cancer **15**:641, 1931.
24. Fischer: Frankfurt. Ztschr. f. Path. **12**:422, 1913.
25. Ryrie, B. J.: Brit. M. J. **2**:1000, 1932.
26. Holden, E., and Gray, J. W.: J. Bone & Joint Surg. **16**:401, 1934.

or destruction by nonsurgical methods forms the basis of the wide impression that a single trauma may transform a benign mole into a malignant melanoma. A careful scrutiny of the evidence in such cases does not support this view, but indicates that the mole was already malignant. The good results obtained by dermatologists with thousands of moles show that when the mole is benign excision or local destruction is a safe procedure. Experience at the Memorial Hospital for the Treatment of Cancer and Allied Diseases shows that nearly always when a patient requests the removal of a mole it is because the mole shows signs of growth, and when removed it is, with very rare exceptions, already malignant and requires careful and wide excision. The clinical histories of nearly all malignant melanomas indicate that the causes of malignancy reside in the original structure and tendencies of the moles and are not connected with traumas except in very rare cases. This principle holds particularly with melanomas of mucous membranes and internal organs. For the same reasons when a long-standing mole on an exposed position becomes malignant the presumption should be that the change results from inherent tendencies and not from the effects of a single trauma. The majority of such moles never become malignant. Evidence is beginning to appear that the growth tendencies of moles are controlled by the sympathetic nervous system and by internal secretions.

In the case of a complicated wound and that of repeated traumas the conditions are radically different, and it appears that melanoma may result from each of these types of injuries either in preexisting moles or even in normal tissues, in subjects with a local or general predisposition. The rarity of such cases indicates that the predisposition is uncommon.

Schopper [27] collected from the literature and his own experience 25 cases in which subungual melanoma followed severe injury with infection or an avulsion of the nail and a variable period of chronic inflammation. He thought a nevus need not precede the melanoma.

Reviewing these cases I find it difficult to determine just what part was played by the injury. In a case of apparently mild blunt injury the thumb-nail was split its entire length. The split remained unhealed for five months and then a slowly progressive growth of tissue appeared, with ulceration and later melanoma. The patient's hands were daily exposed to quicklime, and the unusual result of the slight initial injury suggests some previous pathologic condition in the nail bed. In another case the patient ran a splinter under the nail; the wound never healed, and one and a half years later melanoma was recognized. This brief report relates only to those facts favoring a traumatic origin. Schopper referred to many spontaneous subungual moles and melanomas with

27. Schopper, W.: Centralbl. f. allg. Path. u. path. Anat. **49**:195, 1930.

much the same history as the traumatic ones, reported by Heller and by Rockock. He concluded that trauma alone is incapable of producing subungual melanoma; that infection must be added. In a series of cases of subungual melanoma, Adair and Pack [28] were not impressed with the importance of trauma; nearly all their cases presented definite signs of an active process without trauma.

I have an impression that many of the very malignant carcinomas of the skin following repeated traumas or complicated wounds are melanomas:

A young baseball catcher repeatedly injured the thumb; a fissure developed which did not heal and, after two unsuccessful efforts at surgical removal over a period of six months, was found to have a cellular melanoma with metastases in the cubital lymph nodes.

A young girl suffered from excoriation of the skin of the heel from a misfitting shoe. A horny wart developed after a few months, which progressed rapidly, recurred promptly and produced general metastases. The structure was that of a highly cellular, slightly pigmented melanoma.

A man allowed a projecting nail in his shoe to irritate the sole of his foot for several months. Soon about the fine central punctured point there was pronounced pigmentation of the skin extending superficially over a square centimeter. The biopsy showed melanoma. The patient denied that any mole existed there previously, and stated that the pigmentation appeared only after several weeks. It is said that many of the barefooted Sudanese natives suffer from melanoma of the sole of foot after thorn pricks (Dawson).

Ocular Melanoma.—The state of opinion regarding the traumatic origin of ocular melanoma is well reflected in the report of a case by Stieren and the subsequent discussion of it. The patient received a lacerated wound of the conjunctiva and adjacent tissue which healed normally in two weeks. Nine years later he appeared with a small melanoma on the side distal to the injury, with detachment of the retina. In spite of the absence of any definite signs of injury to the eyeball, the unsatisfactory location of the tumor on the opposite side, the very long interval of time, the history of ocular disturbance for only six months and the absence of any attempt to trace the possible mode of action of the trauma, it is stated that Segond's postulates are fully met and that the case must be accepted as traumatic. This conclusion was vigorously rejected by Verhoeff, who analyzed the case, pointed out the various deficiencies in the evidence and reported that in the examination of over 300 cases of ocular melanoma he had never seen any evidence of trauma. Bancroft followed with the usual clinical statistical report that of 126 patients with ocular melanoma, 9 gave a history of trauma but admitted that the relation of trauma may have been incidental.

28. Adair, F. E., and Pack, G. T.: Bull. Assoc. franç. p. l'étude du cancer **19**:549, 1930.

All objections to the theory that cutaneous melanoma is traumatic apply with added force to the theory that intra-ocular tumors are. Ophthalmic literature would be much enriched by a single report of a case of ocular melanoma in which the known conditions of origin are fully considered, the effects of an authentic and adequate trauma are clearly stated, the probable relation of the trauma to the melanoma is carefully traced, the interval of time is shown to be satisfactory, the gross anatomy and structure of the tumor are demonstrated to be consistent, and all the facts required for an adequate medicolegal opinion and pointing beyond reasonable doubt to the traumatic origin of the melanoma are provided.

Glioma of the Brain and Cord.—The traumatic origin of glioma of the brain and cord has been discussed extensively for many years, and opinions regarding its frequency and the mode of action of the injury have varied widely. Adler [29] collected 1,086 instances of glioma of the brain. Of these gliomas, 8.8 per cent had a rather definite history of having been preceded by trauma. The critical study of Parker and Kernohan [30] showed that of 491 patients with glioma of the brain, 4.8 per cent could be considered as having gliomas possibly of traumatic origin, although a history of previous injury to the skull was obtained from 13.4 per cent. Yet, of an equal number of other patients, 10.4 per cent gave a history of severe injury to the skull, and of 200 normal persons 35.5 per cent gave a history of such injury. They also followed 2,858 war injuries of the skull for fourteen years without finding a single tumor of the brain. Vogeler, Ackerman and others [31] reported 2,775 cases of skull injuries followed for many years, in which they found a great variety of neurologic sequels but no tumors. Since there are very few persons who have not at some time suffered a substantial injury to the skull, the history of such an injury at a distant date creates no presumption in favor of the traumatic origin of a tumor.

Beneke [32] argued strongly in favor of the frequent occurrence of traumatic tumors of the brain, relying especially on the doctrine of spastic contraction of the blood vessels as a cause of necrosis of tissue and later of glioma. In his experience 40 per cent of all gliomas had the history of having followed severe or slight injury to the skull, raising a presumption that the tumors were the results of traumas. Even slight injuries or even psychic traumas such as fright or sudden emotion he held must be accepted as causes of brain tumors. The pathogenesis of these traumatic tumors he conceived as follows: At the point of the injury, or at any distant point in the brain, trauma may cause an arterial spasm. This spasm results in ischemic necrosis of brain tissue. On the edges of the necrotic area arises active proliferation of glia tissue which becomes

29. Adler, H.: Arch. f. Unfall. **2**:189, 1897.
30. Parker, H. L., and Kernohan, J. W.: J. A. M. A. **97**:535, 1931.
31. Vogeler, Ackerman et al.: Monatschr. f. Unfallh. **39**:341, 1932.
32. Beneke, R.: Monatschr. f. Unfalh. **39**:49, 1932.

malignant through the action of the products of degeneration, the "necrose hormones" of Caspari, mostly lipoid. He claimed to have been able, by careful histologic examination, to identify accurately the primary area of necrosis and the tumor process arising about it, and thus to have furnished a scientific demonstration of the traumatic origin of the tumor. He stated his belief that in many instances he had been able to determine the rate of growth and the duration of the tumor, and thus had established whether the proper time relation existed between the injury and the tumor. The theory that gliomas arise from tissue rests or other congenital anomalies of structure he rejected as without foundation since no one had ever seen such rests or anomalies.

This sensational doctrine did not long escape challenge. Within a few months Fischer-Wasels [33] submitted Beneke's argument to a merciless analysis. He first asserted the wide scope of the embryonal origin of tumors of the brain, referring to Kornfeld's [34] recent report on the frequency of tissue rests in the brain and meninges. He sharply denied the possibility of determining the age of necrotic foci or the age of tumors from histologic data. He pointed out that injuries to the skull are so frequent that 99 per cent of all tumors of the brain would be attributed to traumas if Beneke's criteria were followed, and yet such tumors are exceedingly rare and did not increase in frequency after the war. Referring to Ricker's doctrine of arterial spasm following trauma, he found that severe trauma, with unconsciousness, may induce irritability and spasm but, as Ricker stated, never necrosis. In migraine and epilepsy there is severe arterial spasm but no necrosis. The idea that mild injury or psychic shock can produce necrosis he rejected as wholly lacking foundation. He pointed out that tumors never develop about anemic infarcts or other necrotic foci but only about old scars and after a long period of regeneration. Finally he cited a case in which nine years after a gunshot wound of the brain a large glioma developed about the scar tissue, and he accepted the traumatic origin of such a tumor arising under such circumstances and as long as from one to twenty years after the injury, but not of such a tumor arising within one year.

One of the most significant features of this debate was the fact that in one of Beneke's cases an experienced observer accepted without question the statements of the claimant, which strongly favored a traumatic origin of the tumor, although, when the clinical facts were secured, the occurrence of severe cerebral attacks before the accident was established and the traumatic origin was clearly excluded.

Accordingly, for tumors of the brain, one may not relax in any way the rigid criteria of a traumatic origin. When it can be shown that the tissues of origin were lacerated, that the tumor arose in the injured area after an interval sufficient to permit the occurrence of regenerative processes, and that the tumor is of ordinary gliomatous type or other suitable structure, a traumatic origin may be entertained. Rare cases meeting these requirements have undoubtedly occurred and have been reported. It is especially in the scars of injuries that such tumors arise (Beneke; [32] Fischer-Wasels; [33] Reinhardt; [35] Neubürger [36]).

33. Fischer-Wasels, B.: Monatschr. f. Unfall. **39**:520, 1932.
34. Kornfeld, M.: Virchows Arch. f. path. Anat. **278**:165, 1930.
35. Reinhardt, G.: München. med. Wchnschr. **75**:399, 1928.
36. Neubürger, K.: München. med. Wchnschr. **72**:508, 1925.

Cancer of the Breast.—It has long been known that mammary cancer never arises in a normal breast but always on the basis of previous anatomic alterations. These structural alterations take a great variety of forms: chronic cystic mastitis, fibrous atrophic mastitis, simple atrophy of fat, scars of old abscesses, displaced islands of gland tissue, atypical recurrent fibro-adenomas, eczema of the nipple, catarrhal inflammation of the nipple and terminal ducts, tight nipple and papillomas of the ducts.

These abnormalities adequately account for the occurrence of the vast majority of mammary cancers, anatomically considered. However, since cancer often fails to develop on these lesions it has been necessary to determine some other exciting factors. One of these factors has long been recognized in the presence of stagnant secretion in the cancerous focus and generally throughout the breast. The theory that cancer may be due to stagnation of secretion has received substantial support in recent years from pathologists and clinicians. It has been shown, especially by Adair,[37] that cancer of the breast is much more frequent in childless women. In practically all cases of the ordinary forms of mammary cancer I find stagnant secretion in such relation to the cancer as to suggest strongly that the cancer arises as the result of local irritation of the tissues by the altered secretions. Cheatle and Cutler [38] showed in large sections of the breast the mode of origin of the lesion which obstructs the ducts.

In recent years experimental studies have thrown much light on the mode of origin of mammary cancer. Bagg [39] produced mammary cancer in a high proportion of female mice by removing the young at birth or by ligating the ducts on one side and allowing the young to suckle on the other side. Cancer developed in the nonnursing breasts, and on the ligated side only, and as a rule rather promptly. Bagg attributed the results to functional hyperactivity and stagnation. The factors of functional hyperactivity and stagnation have received impressive evidence from the work of Murray, Lacassagne,[40] Little and others who have produced mammary cancer by implanting portions of ovarian tissue in male mice. In many cases the male breasts became hypertrophied and distended with secretion, and cancer resulted.

There is thus an extensive body of evidence showing that cancer of the breast develops under rather peculiar and specific conditions, readily demonstrable, and that in the absence of these conditions the disease does not appear. Therefore, in all cases of cancer of the breast

37. Adair, F. E.: New York State J. Med. **34**:61, 1934.

38. Cheatle, G. L., and Cutler, M.: Tumors of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, Philadelphia, J. B. Lippincott Company, 1931.

39. Bagg, H. J.: J. Cancer Research **9**:498, 1925.

40. Lacassagne, A.: Compt. rend. Soc. de biol. **114**:427, 1933; **115**:937, 1934.

alleged to be traumatic search should be made for some of the aforementioned conditions, and when they are found the conclusion that the disease depends on these conditions and no others rests on a substantial basis. Moreover, the various efforts to produce cancer in lower animals by traumatizing the breast (Lubarsch, Ribbert and others) have uniformly failed.

Marsh [5] attempted to affect the incidence of spontaneous tumors in breeding female mice by mechanically injurying the mammary tissues at three day intervals. Two series with 18 young breeders in each were used. In one series each mouse was injured on the right side only; in the other series, on the left side only. The injury was continued regularly throughout the lives of the animals save for intermissions to allow recovery from the lesions. Breeding was interfered with, and the period of life was shortened to an average period of less than nine months. These conditions and the development of only 3 tumors where many were normally to be expected marked the experiment as a failure.

Nevertheless, medicolegal practice meets a different problem in determining the influence of trauma in cases of mammary cancer alleged to be traumatic. When a woman states that she received a severe blow on the breast followed by pain, swelling and discoloration, that the symptoms persisted for a period of weeks or months, with or without a symptomless interval, and that cancer later appeared at the point of injury, the possible importance of the injury may be dismissed only after a careful application of all the criteria demanded for the establishment or exclusion of a traumatic origin. The inquiry, therefore, involves a laborious program of finding facts.

The authenticity of the trauma may not rest on the mere statements of the patient, but must be corroborated by eye-witnesses and by attestations preferably by a physician as to the signs of injury. The trauma must have been adequate to produce some structural alteration in the breast and must have been attended at least by hemorrhage. The innumerable mild blows which every woman's breast sustains can hardly affect breast tissues protected by a layer of fat from ½ to 1 inch (1.3 to 2.5 cm) thick.

The tumor must arise at the exact point of the injury, since transmitted effects may be excluded in the average breast. The probability of coincidence is very great, and when a mild blow produces unusual pain the previous existence of a tumor at that point should be suspected. Most cases in which cancer of the breast is alleged to be traumatic may, beyond a reasonable doubt, be dismissed if the cancer arises in a segment of breast which is the seat of old chronic fibrous or cystic mastitis or other predisposing anatomic change. There is no definite evidence to show that a trauma to a lesion of this type may precipitate a cancerous process; it is just as likely to be followed by cicatrization.

The only type of mammary cancer that can reasonably be referred to trauma is carcinoma simplex, which conceivably may grow from ruptured ducts into scar tissue. Diffuse duct carcinoma, adenocarcinoma arising in cysts, embryonal cancers, carcinomatous fibro-adenomas, inflammatory carcinomatosis and Paget's disease are not reasonably explained by traumas.

The time factor excludes may alleged cases. Scirrhous cancer does not appear within a few weeks. In the less malignant adenocarcinomas the lymph nodes are not usually involved within a year. Except in the more malignant types, adherence of the skin to the tumor does not occur for some months. There is always a period of some weeks or months when mammary cancer fails to give symptoms.

Therefore, in each case, the entire clinical history must be secured, and the tumor and the entire breast must be examined by a competent tumor pathologist before the basis can be laid for an opinion. When all the data mentioned are carefully gathered and analyzed, it has been my experience that cases of mammary cancer in which a traumatic origin can be reasonably accepted are extremely rare.

At the present time the attitude of the general surgeon toward the traumatic origin of mammary cancer is very uncritical, and the finding of the facts is replaced by unwarranted assumption and speculation. That even experienced observers may fall victims to self-deception is illustrated by the following case, originally reported by Rasch [41] and cautiously interpreted by him as an instance of traumatic cancer, but later repeatedly cited as such in German periodicals:

> In March 1929 a woman of 64 years suffered a puncture wound in the midsternal line from a wire which was wrapped around a small bunch of flowers. Three days later a physician found about the wound a reddish area 0.5 cm. wide. In the following weeks (exact dates not given) a reddish discoloration appeared in the skin of the breast (exact location and extent?). Treatment with x-rays for three days was without effect. By September the patient had lost appetite and was much reduced in strength, and the process had extended to the other breast and down to the navel. No definite sign of a tumor could be found either in the breast or in the skin. The axillary nodes became enlarged (date not given). Death occurred in June 1930. Sections of the skin showed the characteristic highly malignant structure of diffuse duct carcinoma, which infiltrates the dermal lymphatics. The entire picture was typical of diffuse inflammatory duct carcinoma in which there is no localized tumor of the breast, but in which there is rapid dissemination through the skin with an erysipeloid reaction. The wire puncture may possibly have added a local inflammatory element to a preexisting diffuse carcinoma, but it could not possibly have originated the growth of the carcinoma since there is no breast tissue in the midline of the sternum. For the reader the deception was complete when over the puncture point a circle of white dressing was placed fastened by four radiating lines of white rubber plaster that rivet the eye and preclude further scrutiny of the case.

41. Rasch, C.: Brit. J. Dermat. **43**:351, 1931.

Carcinoma of the Lung.—Clinical medicine assigns, as etiologic factors in carcinoma of the lung, tuberculosis, influenza, productive and interstitial pneumonias and exposure to irritating gases, including possibly petroleum products. The Schneeberg miner's cancer may be due to radium rays. These diseases satisfactorily account for the observed cases, and few modern authors mention trauma. Adler [41a] found among 384 cases 6 with a record of previous trauma, but the reports are not impressive and are of the usual clinical type. I should also reject the cases of Aufrecht [42] and Curran.[43] Lepine [44] in 1903 gave a short but rather specific account of a case which may well have been of traumatic origin and which illustrates the conditions under which such an origin may be considered:

> A man of 60 years, previous history not given, was struck on the seventh and eighth ribs in the posterior axillary line by a moving wagon, which produced a prompt contusion. There was no hemoptysis, and in the interval symptoms were lacking. One year later he appeared with cancer of the lung, which became gangrenous and was soon fatal. The autopsy disclosed a squamous cancer of the lung, mandarin size, opposite the point of injury and the pleura adherent to this point. There was a perforation of the chest between the seventh and eighth ribs, and the pleura was concentrically thickened about the sinus.

I have investigated several cases in which pulmonary cancer was alleged to be traumatic, but failed to find any definite indication of such a relation. In most of these cases, the tumor, as usual, was located at the root of the lung, and in none was it primary at the area alleged to be the site of trauma.

Gastric Cancer.—The anatomic features of beginning gastric cancer and its general etiology are rather well known, and they are incompatible with a traumatic origin.

Versé [45] described 12 small, unsuspected gastric cancers discovered at autopsy. The tumors were single, occasionally multiple, slightly raised circumscribed adenocarcinomas, generally infected, eroded or slightly ulcerated and from 0.5 to 2 cm. in diameter. I have seen 3 such lesions. They represent about all that is positively known about the origin of the ordinary form of this disease. In another rarer group of cases the lesion first consists of a focal rather diffuse hypertrophy of lining cells with multiple superficial adenocarcinomatous areas tending to ulceration. This same diffuse process extending over a rather wide

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41a. Adler, I.: Primary Malignant Tumors of Lung, New York, Longmans, Green & Co., 1912.

42. Aufrecht, E., in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1899, vol. 14, pt. 2, p. 362.

43. Curran, W.: Lancet **2**:258, 1880.

44. Lepine: Lyon méd. **100**:18, 1903.

45. Versé, M. A.: Arb. a. d. path. Inst., Leipzig, 1908, vol. 1, pt. 5.

area may affect the chief cells of the glands giving rise to the superficial small cell variety of cancer. In a few cases gastric cancer arises from isolated islands of gastric mucosa lying in the mucosa or the submucosa. Cardiac cancer probably results from a similar heterotopia of gastric or esophageal mucosa at the cardiac orifice.

Cramer [46] summarized the present statistical knowledge of the occurrence of gastric cancer with the conclusion that the disease is dependent on extrinsic factors connected with the dietary habits of the people. One has thus a very comprehensive body of evidence which fully accounts for the occurrence of gastric cancer apart from trauma.

It is not surprising, therefore, that the efforts of occasional authors to establish the traumatic origin of certain gastric cancers have not succeeded and have not received serious attention. Probably the most ambitious of these efforts was that of Menne [47] in 1905. I have studied this contribution carefully on two occasions and failed to find in it any tangible evidence of a traumatic origin of his cases or, indeed, any competent effort to secure the facts in the cases. He endeavored to show that single trauma may directly originate gastric cancer, may accelerate the growth of a preexisting cancer, or by "depleting the system" may hasten the course of the disease, to prove which he relied largely on speculation and assumption. The claims of a traumatic origin in two of his most striking cases were vigorously contested by competent pathologists.

Since it is well known that a severe nonpenetrating wound may cause laceration of the gastric mucosa, it is necessary to consider under what conditions it may be assumed that such an injury has actually been sustained. Here the authenticity and adequacy of the injury must be properly attested. Persistent pain must result, and vomiting of blood is very common. That such contused or lacerated wounds of the stomach have ever produced cancer has never been proved and is highly improbable.

An important observation by Luckow [48] shows that trauma does not render the stomach immune to the ordinary form of cancer (cited by Knox):

> A man wounded by shrapnel in 1917 was examined because of gastric pain in 1928; the x-ray photograph showed splinters of metal in the liver, gallbladder and greater curvature of the stomach. Laparotomy disclosed an extensive gastric cancer, which had developed, not around the metal fragments in the greater curvature, but in the pylorus, where such cancers usually arise.

Gastric Ulcer: Stern,[14] in a standard treatise on trauma, entered fully into the relations of trauma to wounds, ulcers and cancers

46. Cramer, W.: Ztschr. f. Krebsforsch. **34**:531, 1931.
47. Menne, E.: Ztschr. f. Chir.- v. Chir. **81**:374, 1905.
48. Luckow: Ztschr. f. ärtzl. Fortbild. **30**:288, 1933.

of the stomach and duodenum. From the extensive data presented it appears that severe blows to the epigastrium may cause lacerations of the mucosa and tears of the muscular coat, that such wounds, with rare exceptions, heal promptly and without sequel, that they are nearly always accompanied by vomiting and usually hematemesis, that ulcers may form in a few days and heal either rapidly or slowly, that chronic ulcers may occasionally develop, in which case the form of the ulcer differs from the true peptic ulcer in showing adhesions suggestive of a primary rupture of the muscularis, that no typical chronic indurated peptic ulcer has been demonstrated to have occurred after trauma, and that no traumatic ulcer has been demonstrated to run the course of ulcerocancer. In this whole discussion one finds much the same uncertainty regarding the facts as in the usual discussion of traumatic cancer.

The subject of gastric cancer he approached cautiously and from a judicial standpoint, first pointing out that neither experts nor tribunals should or do adopt the theory, *In dubio semper pro laeso* (In doubt always favor the injured). Yet when there exists a striking relation in time and location between an injury and subsequent disease, the expert must not reject the probability of such a relation unless his opinion is supported by attested pathologic anatomic facts, experimental data and extensive clinical experience. Yet, after announcing this sound doctrine, he proceeded to review the reports of 2 cases of gastric cancer and 1 case of cancer of the sigmoid which he would accept as traumatic. In so doing, in my opinion, he violated the principles previously adopted:

> In the first case there were no symptoms of injury to the stomach, and the only evidence favoring trauma was the patient's statement that he was well before the injury and sick thereafter. Six months after the trauma, a bulky tumor was discovered, and after eleven months autopsy disclosed an extensive carcinoma of the stomach without unusual features. In the second case symptoms of an injury to the stomach were absent, and no injury was discovered at laparotomy. Yet the expert adopted the theory that while the injury did not originate the tumor it probably accelerated the growth of an existing minimal tumor anlage. The patient with cancer of the sigmoid received a kick in the abdomen; the blow was followed by vomiting and abdominal tenderness, especially in the left pelvic region, which slowly disappeared. After three years the pain returned, and after four years operation disclosed a large carcinoma of the sigmoid without unusual features.

Tumors of the Testis.—With rare exceptions, malignant tumors of the testis arise at the rete testis and grow into and distend the organ. They develop from sex cells probably misplaced and more or less embryonal. These pursue an abortive course of fetal evolution, producing adult and embryonal organs, in the tissues of which a malignant process is commonly engrafted. The inception of the process is probably

similar to that which excites the normal ovum to growth but does not fertilize it. There is no evidence that trauma can initiate such a peculiar process.

There is a rare adenocarcinoma of adult type, described by Bell, which arises in the body of the testis of the adult subject and grows slowly.

The adult teratomas grow slowly, requiring some months to reach a size which demands attention and continuing to grow for two or three years unless interrupted by complications. A malignant carcinoma of the testis grows steadily and sometimes rapidly, generally with pain, and often with spontaneous hemorrhage, which need not be attributed to injury. A silent period of weeks or months precedes the detection of the tumor, which is often masked by hydrocele. The shortest course of a malignant carcinoma of the testis which I have been able to find was eighteen weeks from the detection of a definite tumor mass until the death of the patient from metastases.

The normal testicle, with remarkable facility, escapes injury from all except rapidly moving hard objects. When injured, it always gives a peculiar testicular pain which readily progresses into shock, and the patient does not recover immediately. When the organ harbors a tumor it is easily injured, and pain results from minor blows and simple pressure. Accordingly, many patients date the beginning of the disease from, and assign the origin to, trauma.

I have investigated many cases of tumor of the testis alleged to be traumatic without finding any that was acceptable. Most of the cases were rejected because the injury was due to simple muscular exertion with back strain, and the pain was referred to the back or to the groin. In others, the blow was directed to the groin, thigh or pubes and not to the testis, and testicular pain was absent. In several cases the size of the tumor and its structure showed that it must have antedated the injury, and in a few cases metastases were already present.

The literature contains many reports of tumors of the testis that were supposed to be traumatic, but most of the reports are without definite value. It is both affirmed and denied that the undescended testis is more subject to malignant growth, and the difference does not favor a traumatic origin of such tumors. Wasterlain [49] gave a comprehensive review of the opinions of current authorities, all of whom were disposed to reject the traumatic origin except in very rare cases in which the injury was fully attested and very severe.

He cited a case reported by Lippens:

> A man of 50 years fell on a rail and received a severe contusion of the scrotum with ecchymosis extending to the groin. He experienced violent testicular pain

49. Wasterlain: J. belge d'urol. **5**:149, 1932.

with syncope, exquisite tenderness lasting several days and swelling of the testis. The swelling subsided for two weeks, remained stationary for four weeks, and then hydrocele appeared twice. For twelve weeks the testis remained swollen, and then nodes in the groin were found to be enlarged, with dissemination following in seven months. The microscopic diagnosis was malignant tumor of the testis.

The experimental studies of Michalowsky [50] are of much interest. He subjected both the testicles of the cock to many forms of severe trauma but in 100 birds never produced a tumor. However, when he innjected zinc chloride into the testes he secured 10 tumors in 50 birds, but only during the spring. Bagg verified these results. These experiments show that the testis of the cock is very insusceptible to malignant growth following trauma, but very susceptible when the right irritant is employed. They tell strongly against the traumatic theory of the origin of these tumors.

Hypernephroma.—Stern referred to 2 cases of hypernephroma as of traumatic origin. The first case must be positively rejected because a large inoperable carcinoma of the kidney was found three months after a blow on the flank. Renal tumors do not grow so fast. The second case is of much interest and calls for critical examination:

A man of 33 years, on the night of Jan. 6, 1920, stumbled over some boards and struck his left side below the costal border against an iron object. There was severe transient pain. Next morning there were meteorism and colicky pains, and large masses of blood clot were passed in the urine. After some weeks a similar attack occurred. On February 4, a roentgenogram showed the kidney to be of normal size and without stones. Thereafter occasional hematuria was noted after lifting. On May 22, 1922, there were severe pains in the back. A smooth oval tumor weighing 980 Gm. was then removed from the kidney, and the patient recovered. The tumor was partly adenoma, partly solid, with necrotic areas. (Whether it was renal or adrenal was not stated.) The possibility that this tumor was caused essentially by the injury must be admitted, but the probability rejected.

The claim of traumatic origin of the hypernephroma in this case involves resort to the hazardous and unproved theory that trauma may excite the growth of a silent tissue rest or miniature adenoma, from which this type of tumor is known to arise. The previous good health is of no moment. The details of the accident appear not to have been corroborated. The severe bleeding after an injury of no great severity suggests, not a normal kidney, but one already the seat of a small tumor. The roentgenographer, looking for injury and stones, might readily overlook a tumor. The period of two years represents a relatively short duration for such a large tumor. Such a series of uncertainties and assumptions is hardly sufficient to establish the traumatic origin of any form of hypernephroma.

50. Michalowsky, I.: Virchows Arch. f. path. Anat. **267**:27, 1928.

The lengthy discussions of this subject by Seeliger,[51] Goldstein [52] and Thiem,[53] written twenty years ago, are notable for the profundity of the argument and the superficiality of the fact-finding. They illustrate the futility of attempting to create out of vague possibilities varying degrees of probability.

Ten years later Rückart [54] reviewed 117 cases of hypernephroma recorded in the literature, found 9 in which a traumatic origin was suggested, but concluded that in all these the injury merely called attention to a preexisting tumor. None of these contributions throws any light on the important question: What causes adrenal rests and miniature adenomas of the kidney to start growing?

Today there is considerable evidence that the real factor consists in functional demands directed to the miniature organs from which the tumors arise and carried by hormones, especially those of the pituitary gland, thyroid gland, pancreas and sex glands.

Hyperplasia of the adrenal cortex occurs under many conditions. It appears whenever there is an excess of prolan A, and this condition is observed frequently with the decline of the sex functions or after castration. It is often found in acromegaly. Injections of prolan regularly induce marked hyperplasia of the adrenal cortex. The close relation between the structure and functions of the adrenals and the structure and functions of the testes has been elaborated by Leupold and others. In a patient who had pseudo-hermaphrodism with rudimentary development of the ovaries, Marchand [55] found marked hyperplasia of the adrenal glands and an accessory gland as large as a testis. A marked enlargement of the adrenal glands is sometimes observed in pregnancy (H. Sternberg). Certain cortical tumors of the adrenal gland possess marked masculinizing powers in both sexes (Glynn [56]). The interrelations between the adrenal glands, thyroid gland and pancreas were long ago pointed out by Falta, Rudinger and Eppinger. Schur and Wiesel [57] noted hyperplasia of the adrenal cortex after partial nephrectomy, and it is often observed in contracted kidneys. Marked disturbances of renal function are observed with many abnormalities of the hypophysis and with certain tumors of the adrenal gland. These and many other recent contributions reveal very numerous conditions in which unusual

51. Seeliger: Monatsh. f. Unfallheilk. **21**:52, 1914.

52. Goldstein: Monatschr. f. Unfallh. **22**:193, 1915.

53. Thiem, K.: Monatschr. f. Unfallh. **22**:110, 1915.

54. Rückart: Deutsche med. Wchnschr. **49**:384, 1923.

55. Marchand: Festschrift für Rudolph Virchow zu seinem 71. Geburtstage gewidnet von dem früheren und jetzigen Assistenten des Berliner pathologischen Instituts, Berlin, George Reimer, 1891.

56. Glynn, E.: Quart. J. Med. **5**:157, 1912.

57. Schur and Wiesel: Verhandl. d. deutsch. path. Gesellsch. **11**:175, 1907.

functional demands are positively known to produce adrenal and renal overactivity and hyperplasia, and they leave little justification for introducing the element of trauma into the origin of adrenal and renal tumors.

SUMMARY

Present data confirm the view, long since adopted by pathologists, that a single trauma of normal tissues is incapable of producing a malignant tumor. This principle may not greatly alter the possible importance of the single trauma as an indirect but essential and determining cause of certain tumors.

Delayed healing due to infection, suppuration and chronic irritation by chemicals or foreign bodies is nearly always observed in cases in which a tumor may be referred indirectly to a trauma. Even in such cases it seems necessary to recognize the probable influence of heredity and of local predisposition of tissues. Repeated traumas acting on successively altered tissues are more likely to induce disordered regeneration than is a single injury.

Only those tumors in which the structure represents an exaggeration or a variation of the normal healing process and its sequels may safely be referred to single traumas.

The rapid increase in the number of known cancerigenic agents and the advances in knowledge of the conditions under which tumors ordinarily develop account adequately for the great majority of tumors and restrict greatly the possible scope of the traumatic origin. When any such agent or condition is detected, a presumption is established that the tumor is caused by it and not by a trauma.

The chief task in determining the relation of a trauma to any given tumor is that of laborious fact-finding. The great majority of reports of tumors alleged to be traumatic would never have appeared in the literature if the facts had been competently gathered and evaluated. The laws of psychology demand that the statements of patients and eye-witnesses should be corroborated, the actual and probable immediate effects of the injury attested by competent persons, preferably physicians, and the entire case studied from a broad clinical and pathologic point of view. In the conduct of such a study the various criteria now recognized in medicolegal inquiry must be employed.

The probability of coincidence is much greater than is generally recognized. The innumerable and constantly occurring mild and severe wounds and bruises insure that a large proportion of tumors receive some injury shortly before their appearance or during their course.

The presence of an unsuspected tumor tends to bring about injuries to the tumor-bearing area and to intensify the subjective symptoms and local effects of the injuries. This principle may be designated as traumatic determinism.

That aggravation has occurred may be accepted when an injury introduces into the course of a tumor significant features which do not normally occur in the course of the disease at approximately the same time, and which are deleterious to the patient. It should be recognized that injury often causes temporary complications the effects of which pass in due time without altering the general course of the disease. The idea that injury usually accelerates the growth of tumor cells is not supported by clinical and experimental data, and applies only to severe injuries in advanced stages of the disease.

It is reasonably well attested that trauma may cause the localization of metastases and the appearance of metastases which might not otherwise occur, but only in the advanced stages of malignant tumors, when tumor cells may frequently escape into the blood, at which time the metastases do not alter the course of the disease.

Opinions regarding the possible traumatic origin of any tumor must be based on a full consideration of the location, known conditions of origin, structural peculiarities and clinical course of the tumor in each organ. Generalizations may be invalid or misleading. Such inquiries belong to the broadly trained clinician and to the experienced tumor pathologist.

The interpretation of compensation laws should recognize that a trauma is never the sole cause of a cancer and is often only a subordinate, although determining, cause, that the probability of coincidence is great, that aggravation by injury is rare and difficult to establish, and that many difficulties and uncertainties will surround this subject for a long time to come. Some form of recognition of partial liability seems necessary to meet these conditions. Without it the compensation law becomes a form of sickness insurance against the natural occurrence and ordinary consequences of one of the major causes of disability and the cause of 10 per cent of the deaths.

There is urgent need of more competent detailed analysis of individual cases of tumors that are possibly traumatic, more extensive studies of the effects of traumas on different organs and tissues and more accurate statistical studies of the incidence, course and complications of all forms of benign and malignant tumors.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

BARTONELLA INCIDENCE IN SPLENECTOMIZED BILE FISTULA DOGS. R. E. KNUTTI and W. B. HAWKINS, J. Exper. Med. **61**:115, 1935.

Splenectomized dogs with bile fistula in this laboratory have regularly exhibited spontaneous anemia for certain periods, which was associated with excessive production of bile pigment. In three of four dogs, such anemia has been shown to be associated with the presence in the blood of bodies morphologically indistinguishable from Bartonella canis as described in the literature. Dogs that were simply splenectomized have not shown such periodical spontaneous anemia. Injections of blood containing bartonella bodies into two splenectomized dogs have resulted in destruction of blood for certain intervals, which was associated with the presence in their blood of bodies similar to those in the injected blood. The injection of such blood into a splenectomized dog with a biliary-renal fistula has resulted in a similar picture. Efforts to cultivate bartonella bodies in artificial culture mediums have thus far been unsuccessful. Neoarsphenamine appears to have a specific sterilizing effect in this condition. Feeding the dogs spleen extract appears to have an inhibiting effect on the anemia and on the overproduction of bile pigment.

FROM THE AUTHORS' SUMMARY.

HEMOGLOBIN AND BILE PIGMENT OVERPRODUCTION IN THE SPLENECTOMIZED BILE FISTULA DOG. R. E. KNUTTI and W. B. HAWKINS, J. Exper. Med. **61**:127, 1935.

Destruction of blood associated with Bartonella or with a drug (hydrazine) in dogs with bile fistula yields a large excess of pigment. These dogs form large amounts of new hemoglobin and bile pigment on a diet which permits of little production of new hemoglobin in standard anemic dogs. When the formation and the destruction of hemoglobin occur rapidly and simultaneously, estimations of the percentage of circulating hemoglobin alone, though showing the eventual total increase or decrease of this substance, do not permit one to determine the actual amounts formed or destroyed. It is suggested that the body can produce readily a large amount of the pyrrole aggregate (four pyrrole rings) which may go to form new hemoglobin. At the same time the globin is probably saved from destroyed red cells and turned over into new hemoglobin for new red cells. It is certain that under certain circumstances globin may be a determining factor in the construction of new hemoglobin for new red cells. Knowledge about the construction and internal metabolism of globin is extraordinarily limited.

FROM THE AUTHORS' SUMMARY.

THE ASSOCIATION OF BARTONELLA BODIES WITH INDUCED ANEMIA IN THE DOG. C. P. RHOADS and D. K. MILLER, J. Exper. Med. **61**:139, 1935.

On feeding splenectomized dogs a diet producing black tongue, severe anemia developed associated with the presence of small bodies in or on the erythrocytes. The bodies were morphologically similar to Bartonella muris and Bartonella canis. The addition of lean beef to the diet, a material prophylactic against the effects of the diet, was followed by an improvement of the blood levels, an increase in the numbers of reticulocytes in the circulating blood and the disappearance of the bodies. When the blood containing Bartonella-like bodies was injected into other splenectomized dogs fed a normal diet or one producing black tongue, anemia

developed in these dogs, and the bodies appeared in large numbers. Similar injections into nonsplenectomized animals fed in the same way resulted in anemia alone. Injections into normal animals fed a normal diet did not cause anemia.

FROM THE AUTHORS' SUMMARY.

ENDOBRONCHIAL OCCLUSION. E. C. CUTLER and C. B. WOOD, Surg., Gynec. & Obst. **59**:501, 1934.

In a large series of dogs a 25 per cent solution of acriflavine was found to produce a painless, aseptic and complete occlusion of any bronchus, first by the formation of a firmly adherent mucoid plug, which later separated and was coughed out, and subsequently by a peribronchial and submucous fibroblastic proliferation with resultant fibrosis and contraction. Pulmonary atelectasis was accomplished only when all bronchi leading to the lobe were completely closed. Microscopically, the airless lung showed no evidences of pneumonitis at any stage. Permanent atelectasis was compatible with normal health and well-being of the animals even though all bronchi to an entire lung were closed. W. C. HUNTER.

AIR EMBOLISM. W. H. CHASE, Surg., Gynec. & Obst. **59**:569, 1934.

During an attempted lobectomy for bronchiectasis the main pulmonary vein was accidentally cut. Immediately there followed a brisk hemorrhage accompanied by a whistling inspiratory sound, collapse of the pulse, increase of systolic blood pressure and death within three minutes, although the severed vessel was clamped within fifteen seconds. Macroscopically visible air emboli were present in most of the larger arteries of the brain and in the coronary arteries of the heart. Histologically there was marked engorgement of the meningeal veins, which were sometimes collared by fresh hemorrhage, particularly those displaying partial disintegration of their walls. Periarterial hemorrhages were absent.

In order to obtain more information about the vascular mechanism in air embolism air of the room was injected into the arteries of rabbits, and the effects on the mesenteric vessels were studied both in vivo and microscopically. In the muscular arteries the injected air tended to remain in long columns; it was slow to enter the arterioles and break up in them, and never passed beyond the latter. The air failed to exercise any definite coagulative or agglutinative action on the erythrocytes. On the other hand, the blood moved rapidly through the arterioles after the air passed on. Two distinct vascular effects, traumatic and mechanical, followed the introduction of air. The first of these was on a neurovascular basis, independent of the nature of the irritant, and produced an immediate transient vasoconstriction of the muscular arteries involved during which the slow peripheral movement of the blood was associated with slight diapedesis. Fatigue of the muscular arteries translated the vasoconstriction into vasodilatation and progressive arterial hyperemia. The mechanical vascular effect was due to air obstructing small arteries and arterioles, which likewise caused rapid and prolonged peripheral prestasis, and during this interval more or less abundant diapedesis of red cells took place from the venous side of the terminal segments, ending usually with complete cessation of blood flow. Hemorrhages were abundant about venous channels but never occurred around muscular arteries. Ricker's observations on the effects of other vascular irritants are corroborated by these experiments. Most of the many contradictions in the literature as to the cause of death in air embolism are due to differences in the resistance of various animals to air emboli. Death may be ascribed to impairment of heart function and to sudden loss of function of some vital center of the brain due to vasoparalysis with stasis. W. C. HUNTER.

EXPERIMENTAL CHRONIC INTESTINAL OBSTRUCTION FROM BLIND LOOPS. H. E. PEARSE JR., Surg., Gynec. & Obst. **59**:726, 1934.

In a series of dogs entero-enterostomy was done for internal drainage in intestinal obstruction, leaving a blind segment between the anastomosis and the point of obstruction. The blind segments were of varying lengths. Their fate

depended on the direction of peristalsis and their length. Below the obstruction the bowel remained empty and functionless, but above this point, when the peristaltic current was directed from the anastomosis toward the blind end, material was carried in and retained. Loops less than 1 foot (30.5 cm.) long emptied themselves and did not dilate. Those 2 feet (60.9 cm.) long became dilated and filled with inspissated contents but caused no clinical symptoms. When the length was increased to from 3 to 4 feet (91.4 to 121.9 cm.) there occurred a filling with condensed material, marked hypertrophy and dilatation and after from three to four months chronic intoxication, leading finally to death without evidence of mechanical obstruction or disturbances in the blood chemistry. Resection of such loops was followed by full recovery. When loops from 5 to 6 feet (152.4 to 182.8 cm.) long were made the dogs died of inanition and dehydration as a result of inadequate absorptive surface. Pearse prefers entero-enterostomy to enterostomy in human beings when it is inadvisable or impossible to remove the cause of the obstruction and has employed the procedure successfully in two instances in which it was possible to make short loops.

FROM THE AUTHOR'S SUMMARY [W. C. HUNTER].

CHOLINE AND LIVER FAT. D. L. MACLEAN and C. H. BEST, Brit. J. Exper. Path. **15**:193, 1934.

In some as yet unexplained way choline prevents the deposition of fat in the livers of diabetic dogs or normal rats under the conditions of the experiments described in this paper. There is no evidence that choline affects the phagocytosis of fat particles. Rats which have received adequate amounts of choline in addition to fat exhibit no histologic abnormalities in the liver cells.

FROM THE AUTHORS' SUMMARY.

HYPERVITAMINOSIS D RICKETS. A. W. HAM and L. D. MURRAY, Brit. J. Exper. Path. **15**:228, 1934.

Young rats receiving very large daily doses of vitamin D showed rachitic lesions in the long bones after three weeks. As the matrix which formed in the bones during the experiment was poorly calcified, it was concluded that the administration of large amounts of vitamin D inhibited the normal process of calcification in the bones. As osteoclasts were not prominent in the histologic picture, the poor calcification could not be attributed to them. The phenomena observed can be explained best, it is thought, by the theory that vitamin D in some way increases the attraction of the blood for calcium. The results are compatible with, although they do not directly support, the theory that vitamin D acts through the intermediary of the parathyroid mechanism to control a fraction of the serum calcium.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL PRODUCTION OF TENDINOUS PATCHES OF THE PERICARDIUM. H. GIRGENSOHN, Virchows Arch. f. path. Anat. **293**:73, 1934.

This is the sixteenth in the series of contributions based on work carried out under Klinge's guidance in Hueck's institute and devoted to the pathology of rheumatic infection. The frequent association of milky patches of the epicardium with evidences of rheumatic infection suggested that the patches are inflammatory rather than merely mechanical in origin. Rabbits were sensitized against horse serum. From four to five weeks after sensitization, from 1 to 2 cc. of horse serum was injected into the pericardial cavity. The animals were killed and examined from six to thirteen weeks later. In experiments of shorter duration, localized areas of inflammatory reaction characterized by cellular proliferation and formation of new vessels were noted. In experiments of longer duration, such areas had been transformed into fibrous scars like the milky patches of the human heart. Adhesion of the two pericardial layers did not occur, a finding that answers the older objection that the tendinous patches cannot be inflammatory in origin because they never lead to pericardial adhesions. The inflammatory origin of milky patches

having been experimentally established, Girgensohn concludes that the frequent association of such patches with evidences of previous rheumatic infection is proof that this infection is the most frequent cause of tendinous patches of the pericardium.

O. T. SCHULTZ.

THE SITE OF FORMATION OF GONADOTROPIC SUBSTANCE IN THE URINE IN PREGNANCY. T. REMZI, Zentralbl. f. Gynäk. **58**:1962, 1934.

The fact that the gonadotropic hormone in the urine is especially profuse in cystic mole and in choriocarcinoma suggests that the hormone may be of chorionic origin. Remzi reports two cases, one of cystic mole and one of choriocarcinoma, in which the urine was rich in hormone and in which parts of the mole and of the choriocarcinoma gave the Aschheim-Zondek reaction while the anterior lobe of the hypophysis did not.

RELATIONSHIP BETWEEN VITAMIN B AND THE PROTEIN, FAT AND CARBOHYDRATE OF THE DIET. P. VOGT-MØLLER, Copenhagen, Levin & Munksgaard, 1934.

The object of these studies was to determine whether there is a relation between the amount of vitamin B and that of protein, fat or carbohydrate in the diet. Mice were fed controlled diets as follows: a standard normal diet, a diet rich in fat, a diet high in carbohydrate, one high in protein, and one high in vitamins such as A and D in the form of cod liver oil, B complex in the form of dried yeast, B_1 and B_4 in the form of tikitiki extract and vitamin E in the form of wheat germ oil. The weight and growth of a great number of male and female mice on the particular diets was studied from the twenty-first day to the thirtieth week of life. With a diet rich in fat the animals seemed to need less vitamin B_1, while their requirement of B_2 was increased. On a diet rich in fat supplemented with vitamin B_1 the animals soon acquired mild symptoms of pellagra before their premature death. With a diet high in carbohydrate the requirement of vitamin B_1 or B_4 was increased. If these animals did not receive the vitamins in question, death occurred earlier than with a well balanced diet or even one high in fat. None of the animals on the diet high in carbohydrate showed symptoms of pellagra.

It is concluded that vitamin B_1 (plus B_4) bears a quantitative relation to the carbohydrate content of the diet. When the amount of carbohydrate is increased, the need for vitamin B becomes greater. Vitamin B_2 bears a similar relation to the fat content and probably to the protein content of the diet. With a diet rich in fat less vitamin B_1 is required than with a well balanced diet or one high in carbohydrate. The quantitative requirements of vitamin B complex are influenced by the composition of the diet. This should be considered in comparative studies on vitamins.

JACOB KLEIN.

Pathologic Anatomy

THE PATENCY OF THE SO-CALLED "ANATOMICALLY OPEN BUT FUNCTIONALLY CLOSED" FORAMEN OVALE. PAUL GROSS, Am. Heart J. **10**:101, 1934.

Under a preponderance of pressure in the right atrium as compared with that in the left, pressure, fluid and emboli may be transmitted from the right atrium through the foramen ovale into the left atrium. When the left auricular pressure is greater than the right, comparatively little or no transmission of pressure or fluid from the left to the right atrium occurs, owing to a valvelike action of the foramen ovale.

AUTHOR'S SUMMARY.

CALCIFICATION OF THE MYOCARDIUM FOLLOWING CORONARY OCCLUSION. F. J. HIRSCHBOECK, Am. Heart J. **10**:264, 1934.

An instance of myocardial calcification subsequent to coronary occlusion is reported, in which the plaquelike calcification involved the area of the heart muscle supplied normally by the occluded descending branch of the left coronary artery.

AUTHOR'S SUMMARY.

CONGENITAL HYPERTROPHY OF THE MUSCLES, EXTRAPYRAMIDAL MOTOR DISTURBANCES AND MENTAL DEFICIENCY. CORNELIA DE LANGE, Am. J. Dis. Child. **48**:243, 1934.

A clinical entity exists in which congenital muscular hypertrophy, extrapyramidal motor disturbances and mental deficiency are found. Three children whose families were not related came under observation at the Children's Clinic of the University of Amsterdam, The Netherlands. The report of a fourth case was found in the literature. In one case, extensive postmortem examination of the brain was possible. Macroscopic examination revealed polygyria and extensive microgyria, most marked in the occipital lobes. Section showed a moderate communicating hydrocephalus. There was overdevelopment of the gyrus supramarginalis and gyrus angularis, and the paleocerebellum was well developed as compared with the small neocerebellum, thin corpus callosum and broad fornices. There proved to be hypertrophy of the nucleus basalis and substantia innominata, the superior olives and the corpus trapezoideum and a peculiarity in the loops of the inferior olives. Microscopically a porencephalic process was found widespread in the cerebral hemispheres.

RALPH FULLER.

THORACIC AORTIC ANEURYSMS IN CHILDREN: THEIR RELATION TO RHEUMATIC FEVER. J. K. CALVIN and S. J. NICHAMIN, Am. J. Dis. Child. **48**:780, 1934.

Two cases of spontaneous rupture of the thoracic aorta in children aged 11 and 4 years, respectively, are reported; in one case, the rupture was proximal to coarctation of the aorta, diagnosed during life, and in the other the rupture was through an aneurysmal sac into the pericardium. In both cases, verrucous aortitis was the primary pathologic condition leading to the rupture.

FROM AUTHORS' SUMMARY.

OSTEOPETROSIS (MARBLE BONES) IN AN INFANT. D. J. MCCUNE and C. BRADLEY, Am. J. Dis. Child. **48**:949, 1934.

Osteopetrosis (osteosclerosis fragilis generalisata) is characterized by increased thickness and density of the cortical and spongy portions of the bones. The marrow cavity may be encroached on to the point of obliteration, and there are frequent alterations in the external configuration of the bones. Roentgenographically the bones appear opaque, heavy and lacking in finer structure. These changes may be associated with a myelophthisic type of anemia. There may be multiple pathologic fractures, chronic osteomyelitis, hydrocephalus, optic atrophy and enlargement of the liver, spleen and lymph nodes. The disease shows a striking familial tendency and is occasionally hereditary. It is a rare disease. Sixty-seven cases have been reported in the literature, and to this number McCune and Bradley add a new case.

SUBACUTE PERIBRONCHIOLAR PNEUMONIA. HERBERT S. REICHLE and ALAN R. MORITZ, Am. J. Dis. Child. **48**:1001, 1934.

Subacute recurrent peribronchiolar pneumonia is a disease of infants which has a characteristic composite of signs and symptoms. The history of repeated or continuous respiratory disease, the typical cough and the widespread obstruction of the smaller bronchioles make it possible to diagnose the condition during the life of the patient. In eight of fourteen cases permission to perform an autopsy was obtained, and the autopsies substantiated the clinical diagnoses. Exudate and proliferative changes were found in and around the smaller respiratory passages, whereas the alveoli were relatively free from inflammation. Little can be said concerning the etiology of the disease. It is probably a respiratory infection caused by common micro-organisms which localize at a site that has mechanical disadvantages for an infant otherwise possessing considerable resistance.

AUTHORS' SUMMARY.

ENLARGEMENT OF THE HEART DUE TO ABNORMAL STORAGE OF GLYCOGEN (VON GIERKE'S DISEASE). W. ANTOPOL, J. HEILBRUNN and L. TUCHMAN, Am. J. M. Sc. **188**:354, 1934.

Deposition of glycogen may occur in the liver, kidneys, brain, heart, blood vessels, muscles and organs of internal secretion. The clinical picture depends on the sites of deposition and on the extent to which the vital processes of the affected tissues are involved. So far three main groups of symptoms are known, based on a preponderance of deposits in the liver and kidneys, in the heart and blood vessels and in the brain, respectively. The first group is the best known and possibly the largest—that of glycogenic hepatonephromegalia of von Gierke. The second group—that of cardiac hypertrophy—gives a clinical picture which, in the absence of proper chemical and histologic studies, may be confounded with that of so-called idiopathic hypertrophy of the heart. It is possible that many of the cases formerly classified as examples of idiopathic hypertrophy belong to the von Gierke group with enlarged heart, and that rhabdomyoma is a localized collection of glycogen-rich fibers, possibly the result of a focal disturbance in the metabolism of glycogen. The third group, that of symptoms due to deposits of glycogen in the brain and spinal cord, makes necessary a review of all poorly understood cerebral conditions in children in order to determine whether some of them are not related to the effect of an abnormal storage of glycogen. FROM AUTHORS' SUMMARY.

ELONGATION OF THE RED BLOOD CELLS. LEO H. POLLOCK and WILLIAM DAMESHEK, Am. J. M. Sc. **188**:822, 1934.

Large numbers of oval, elongated and sickle-shaped red blood cells were found in three members of a Jewish family in whom no admixture of Negro blood could be elicited. The greatest number of abnormally shaped red cells appeared forty-eight hours after the blood was drawn. At the temperature of the incubator, the rate of anisocytosis was slightly increased; at that of the refrigerator, it was definitely diminished. Pressure probably caused the development of elongation somewhat more rapidly in cells which already possessed the tendency latent. No definite effect was produced by roentgen rays or by anticoagulants. The abnormally shaped red cells were found to be slightly more fragile than normal cells. Potassium cyanide, carbon dioxide and nitrous oxide produced an increased development of abnormal red cells. Trinitrophenal caused some of the oval forms to become rounded. No effect was noted with oxygen. The greatest proportion of abnormal cells was found in a patient in whom the red cell count dropped to 2,610,000. It is probable that oval, elongated and sickle-shaped red cells and sickle cell anemia represent various gradations in the same general abnormality of red blood cells. The significance of certain observations made on the red cells in vitro is questioned. The most important factor in the pathogenesis of the disorder appears to be that of heredity. The appearance of oval, elongated and sickle-shaped red blood cells in members of the white race cannot longer be questioned.

FROM THE AUTHORS' SUMMARY.

A STUDY OF THE SPUTUM IN PULMONARY ASBESTOSIS. ROBERT C. PAGE, Am. J. M. Sc. **189**:44, 1935.

Asbestos bodies in the sputum are indicative merely of exposure to asbestos dust. If they are of large size it means that a long interval has elapsed since the onset of exposure. The number of bodies in any given specimen is insignificant, but the presence of old and weathered bodies on repeated examinations strongly suggests that a pathologic process is in existence. Clumps in the sputum are evidence of lung disintegration, but their absence does not mean that disintegration is not in process. Elastic fibers are probably indicative of rapid destruction of the lung. Elastic fibers may be present in the sputum both with and without clumps in cases of pure pulmonary asbestosis and in cases associated with tuberculosis. Routine examination of the sputum in cases of suspected pulmonary asbestosis is essential, as it plays a significant rôle in the clinical diagnosis.

AUTHOR'S SUMMARY.

SPONTANEOUS RUPTURE OF THE ESOPHAGUS IN SYPHILIS. W. EVERETT GLASS and WILLIAM FREEMAN, Am. J. M. Sc. **189**:80, 1935.

Complete rupture of the esophageal wall may occur, in relatively rare instances, as a result of syphilitic periarteritis of the organ and the severe retching and vomiting which are a rather common accompaniment of paretic seizures. A routine detailed examination of this organ in all autopsies is urged. The esophagus is more vulnerable to pathologic lesions than the statistics have heretofore indicated.

AUTHORS' SUMMARY.

THE DISAPPEARANCE OF GLOMERULI IN CHRONIC RENAL DISEASE. A. R. MORITZ and J. M. HAYMAN JR., Am. J. Path. **10**:505, 1934.

The number of possibly patent glomeruli and glomerular scars has been estimated by a method combining injection and histologic examination. The average number of glomeruli in fourteen normal human kidneys was 1,282,800 ± 32,700. In chronic renal disease not only the number of patent glomeruli but the total number of recognizable glomerular structures was reduced. This was most marked in chronic glomerular nephritis. The number of possibly patent glomeruli frequently falls below 500,000, and may be below 200,000. The total number of recognizable glomerular structures, including scars, was frequently below 600,000 and in some instances below 300,000. Since large numbers of glomeruli may disappear during the course of chronic renal disease it is suggested that the final histologic pattern may not give as much information concerning the pathogenesis or severity of the disease as is commonly thought.

FROM THE AUTHORS' SUMMARY.

INCLUSIONS IN RENAL EPITHELIAL CELLS FOLLOWING THE USE OF BISMUTH PREPARATIONS. A. M. PAPPENHEIMER and E. M. MAECHLING, Am. J. Path. **10**:577, 1934.

Refractile globules were found within the nuclei and cytoplasm of renal epithelial cells in two cases following intramuscular injection of bismocymol (a bismuth derivative of camphocarbonic acid) in one instance and following that of potassium bismuth tartrate with butyn in the other. Similar globules were found in the renal epithelial cells of rats after the injection of appropriate doses of bismocymol. The chemical nature of these globules was not determined; they gave equivocal reactions for bismuth, were insoluble in lipoid solvents and in strong alkalis and acids, resisted tryptic digestion, did not give a reaction for iron or calcium but stained as myelin by the Spielmeyer method. FROM THE AUTHORS' SUMMARY.

GLYCOGEN-STORAGE DISEASE. E. M. HUMPHREYS and K. KATO, Am. J. Path. **10**:589, 1934.

Glycogen storage disease (thesaurismosis glycogenica, von Gierke) is a disorder of infancy and childhood, possibly familial, affecting both sexes. It is characterized anatomically by enlargement of organs and the storage of glycogen chiefly, but not exclusively, in the enlarged organs. Two main types have been delimited, glycogenic hepatomegaly, or hepatonephromegaly, and glycogenic cardiomegaly. The affected organs may attain great size and may contain glycogen in unprecedented amounts. One peculiar feature is delayed postmortem glycogenolysis, and the search for glycogen has been successful in spite of adverse circumstances and imperfect technic. In only a few instances has glycogen storage been associated with degenerative or proliferative changes. At least in the hepatomegalic type, clinical studies have seemed to point to an impairment of the mechanisms concerned in the mobilization of glycogen and the regulation of the blood sugar. Less is known of the cardiomegalic type. We present the clinical and postmortem studies of three proved cases and one probable case of cardiomegalic glycogen storage disease. The weights of the hearts were from 3.3 to 7 times the normal, and the

myocardial fibers were enlarged, vacuolated and (in three cases) filled with glycogen. It is probable, though proved in only one case, that the liver and kidneys were affected similarly but to a lesser degree. In two cases the skeletal muscles showed an unusual type of vacuolar degeneration, and in one of these the vacuoles contained much glycogen. This report brings the total number of proved cases to fifteen.

FROM THE AUTHORS' SUMMARY.

ALTERATIONS IN THE MINERAL CONSTITUENTS OF ANTERIOR HORN CELLS IN EXPERIMENTAL POLIOMYELITIS. W. E. PATTON, Am. J. Path. **10**:615, 1934.

The principal type of destruction of nerve cells in poliomyelitis involves three stages: (1) edema, with acute swelling of the cell and diminution of its inorganic content; (2) granulation, with hypermineralization, and (3) acidophilic necrosis, with diminution of the mineral constituents. FROM THE AUTHOR'S SUMMARY.

TUBERCULOSIS OF THE MAJOR BRONCHI. H. S. REICHLE and T. T. FROST, Am. J. Path. **10**:651, 1934.

Tuberculosis of the major bronchi can be classified according to pathogenesis as (1) infection by implantation, (2) infection by contiguity and (3) infection by continuity. The first is decidedly less common than the other two, a fact that may be ascribed to the protective influence of cilia, mucus and bronchial peristalsis. Infection by contiguity is prone to occur because of the proximity of the extracartilaginous mucous glands to diseased lymphatics and lymph nodes. Proliferation of the adventitia and atrophy of the mucous glands tend to close this avenue. Infection by continuity occurs secondarily to an implantation tuberculosis in the lower lobes and in the bronchi draining a tuberculous cavity. Major bronchi appear to be especially resistant to tuberculosis; however, when fibrosis has transformed them into rigid tubes, and the mucosa and submucosa are destroyed and replaced by tuberculous granulation tissue, an open focus of disease is created which is rarely closed either by the natural processes of healing or by pneumothorax or thoracoplasty. We therefore suggest that the critical aspect of a tuberculous cavity is not so much in its size per se, or in the density of its wall, as in its relation to a major bronchus.

FROM THE AUTHORS' SUMMARY.

CALCIFICATION IN THE BRAINS OF EQUIDAE AND OF BOVIDAE. E. W. HURST, Am. J. Path. **10**:795, 1934.

Calcification of the vessels of the globus pallidus is at least as frequent in middle-aged and old horses as in man at a corresponding period of life; it also occurs in cattle. In neither species can it be correlated with the pathologic condition responsible for death. Since similar appearances are met with in monkeys, it seems probable that it may represent a biologic phenomenon of some constancy in advancing life in the higher mammals. Unlike man, many horses, both young and old, show small calcified bodies in the intima of the larger meningeal arteries. Calcification may sometimes be present in other parts of the central nervous system. The use of the purpurin test following treatment of sections with oxalic acid permits recognition of calcium salts in the presence of iron compounds; in the horse both are represented in the degenerated vessels.

FROM THE AUTHOR'S SUMMARY.

THE TRANSFORMATION OF ADIPOSE TISSUE IN EXPERIMENTAL TUBERCULOSIS. G. A. BAITSELL and K. E. MASON, Am. Rev. Tuberc. **29**:587, 1934.

Adipose tissue from the fat body of the guinea-pig testis experimentally infected with tubercle bacilli undergoes rapid and striking histologic changes characterized by the formation of an abundant intercellular exudate. The normal vesicular fat cells disappear and a dense fibrous tissue arises by transformation of the structural elements of the exudate. After a time, cells grouped to form tubercles appear,

and as they enlarge, they are infiltrated and encapsulated by heavy bands of the newly formed fibrous tissue. It is pointed out that the fibrillar elements have their origin in a purely intercellular material formed as a cell secretion. The present results support the view, stated in 1915, that fiber formation in the mature vertebrate is directly connected with fibrin formation in the blood plasma.

H. J. Corper.

Acquired Heart Block with Adams-Stokes Attacks Dependent upon Persistent Ostium Primum. W. M. Yater, C. W. Barrier and P. E. McNabb, Ann. Int. Med. **7**:1263, 1934.

The defect occurred in a woman 67 years of age. She was said to have had rheumatism at the age of 12 and typhoid fever at the age of 30. Following the latter condition she was confined to bed for months with a leaky heart and dropsy. Intermittent heart block with Adams-Stokes attacks and mitral valvular disease existed; also auriculoventricular dissociation. The patient died following a long attack of syncope and convulsions. The heart weighed 505 Gm. The right chambers made up the greater part of the bulk. There was a large defect in the lower part of the interarterial septum, 1.7 cm. in the vertical and 3.2 cm. in the transverse dimension. The fossa ovalis was above this opening and was closed. The medial tricuspid valve made up the lower margin of the defect. The anterior mitral leaflet was continuous with the septal tricuspid valve. Serial sections from the margins of the defect revealed the bundle of His to be slightly displaced and moderately fibrous. No evidence of lesions attributable to rheumatism was found.

Frank R. Menne.

Total Transposition of Viscera in Siblings: Case Reports. Edward A. Gall and Victor F. Woolf, Ann. Int. Med. **7**:1370, 1934.

Complete transposition of the viscera was observed in a 2 year old Negro girl and her 4 month old sister. The authors state that fifteen other cases of transposition of the viscera in siblings have been recorded in the literature.

Frank R. Menne.

External Trauma in Relation to Ulcer of the Stomach and Duodenum. Irving Gray, Ann. Int. Med. **7**:1403, 1934.

Compared with the French and German literature, the American literature contains few reports of cases of traumatic ulcer in the stomach and duodenum. Rehn is quoted as saying that injuries may cause: (1) tears of the serous coat, (2) injuries of the serous muscular coat, (3) hematoma between the muscular layers and the mucosa, (4) tears of the mucosa and (5) complete rupture. Gray reports the following cases: 1. A woman, aged 31, received a severe contusion in the upper part of the abdomen in a taxicab collision; twenty-four hours later she vomited blood and had tarry stools; later she felt pain and distress after meals. Roentgen examination seventeen days after the injury revealed a defect in the pyloric region. This healed after nine months. 2. A man, aged 37, who was struck forcibly in the upper part of the abdomen by a wooden plank, had epigastric pain with discomfort after meals and occasional vomiting twenty-four hours after the accident. Roentgen examination revealed a persistent irregularity on the mesial aspect of the duodenal bulb, which under treatment disappeared two months later. 3. A man, aged 41, was caught between the steering wheel and the body of his truck in an automobile accident. A persistent dull pain developed in the epigastrium about one hour after the noon meal. The stools were tarry during the first week after the accident. Roentgenograms revealed an ulcer two months after the accident. It is concluded (1) that acute traumatic peptic ulcer may follow strong blunt force to the epigastrium, the tendency in such cases being toward complete healing, and (2) that external trauma as a factor in the pathogenesis of chronic peptic ulcer is still a debatable question.

Frank R. Menne.

OSTEOMALACIA. FRANCIS D. GUNN and WALTER H. NADLER, Arch. Int. Med. **54**:145, 1934.

The observations at necropsy in a typical case of osteomalacia in a man are presented and discussed. Besides the typical skeletal deformities, of special interest were hypertrophy and hyperplasia of the parathyroid glands, slight hypertrophy of the anterior lobe of the hypophysis and numerous small calcareous deposits in the kidneys. Only two parathyroid glands could be found. These were equally enlarged and presented microscopic evidence of mild hyperplasia, which was interpreted as compensatory on increased physiologic activity.

AUTHORS' SUMMARY.

LATENT ACUTE RHEUMATIC CARDITIS AS DETERMINED AT AUTOPSY. FRANK HAWKING, Arch. Int. Med. **54**:799, 1934.

Cases are described in which rheumatic myocarditis or rheumatic endocarditis was discovered at autopsy, although the active rheumatic infection had not been recognizable during life. No correlation could be established between the rheumatic disease and any one of the other various pathologic conditions found. It is therefore concluded that the association is accidental. It appears that in addition to those whose condition is diagnosed clinically as rheumatic fever, 1.2 per cent of other patients dying at the Presbyterian Hospital in New York City have rheumatic disease.

AUTHOR'S SUMMARY.

LEUKEMIC CHANGES IN THE BRAIN. ISADORE B. DIAMOND, Arch. Neurol. & Psychiat. **32**:118, 1934.

In fourteen cases of leukemia (myelogenous, lymphatic, myeloblastic, monocytic and stem cell types) a study was made of the cerebral changes. These changes in some cases involved the parenchymal, glial and mesodermal tissues. The parenchymal changes varied from chromatolysis to liquefaction—that is, a complete disruption of the cell body—with neuronophagia and axonophagia. Such changes, which were often associated with focal and diffuse glial and microglial proliferation and swelling of the oligodendroglia, were due to marked leukemic infiltrations in the form of nodules and leukemic invasion of the perivascular spaces. The nodules were sometimes large; often they were small, numerous and coalescing. Small nodules were often overshadowed by hemorrhages; hemorrhages also surrounded larger nodules. Vascular changes were also present in the parenchyma and the pia, and once the longitudinal sinus was involved. An interesting feature was severe infiltration of the perineurial spaces of the cranial nerves, especially those of the seventh nerve and of the optic chiasm. The enormous infiltrations of the lumens of the blood vessels and of their perivascular spaces, with formation of a vast number of nodules, are considered by Diamond as the cause of the parenchymatous changes, either by pressure or by the formation of toxic substances.

GEORGE B. HASSIN.

PRIMARY EPENDYMITIS (OCCLUSION OF THE FORAMINA OF MONRO AND HYDROCEPHALUS OF THE LATERAL VENTRICLES). JAMES G. ARNOLD JR., Arch. Neurol. & Psychiat. **32**:143, 1934.

According to Arnold, primary ependymitis may be considered a condition in which the ependyma, subependyma and choroid plexus are involved by a primary, probably toxic or infectious process. It is rare in contrast to the secondary type, caused by meningitis or a ruptured cerebral abscess. In the case which he reports, an abnormal mental condition (changed personality with defects of memory and increased sexual libido) insidiously developed in a white married man, aged 32. The patient had had a fall followed by unconsciousness for three days at the age of 10, a chancre at the age of 22, which had not been treated, and an acute gastric upset after excessive consumption of alcohol four weeks prior to his admission to the hospital. Neurologic examination revealed a slight weakness of the left side

of the face, bilateral Babinski and Oppenheim signs and enormously dilated lateral ventricles. Necropsy disclosed a marked hydrocephalus with dilated lateral ventricles, a fenestrated septum pellucidum, occlusion of both foramina of Monro by a swollen choroid plexus and a much thickened ependyma. Inflammatory cells—lymphocytes, plasma cells and a few polymorphonuclears mixed with denuded ependymal cells—were everywhere present in the subependymal areas, especially in the region of the foramina of Monro, while the meninges, cortex and subcortex were normal, and the choroid plexus was hyperplastic and involved throughout. Arnold thinks it was probably the portal of entry of some infection or intoxication that had a predilection for the ependymal and subependymal tissues and remained localized.

GEORGE B. HASSIN.

FACIAL AND MENINGEAL ANGIOMATOSIS ASSOCIATED WITH CALCIFICATION OF THE BRAIN CORTEX. KNUD H. KRABBE, Arch. Neurol. & Psychiat. **32**:737, 1934.

Krabbe describes six cases of intracranial calcified angioma. Five of the patients had had epilepsy since childhood and were mentally defective. Some had slight spastic hemiplegia with angioma of the contralateral side of the face. The histologic changes—the first to be recorded—in one patient, who died at the age of 19, were excessive vascularization (but not true angioma) of the pia over the occipito-temporal area and an accumulation of granules of lime salts in the neuroglia of the atrophied and "firm" gyri of the occipital lobe and of part of the temporal lobe. The outer second and third layers were especially involved, as here the ganglion cells were absent; the myelin and blood vessels were normal. Krabbe remarks that the changes in the brain and the "angiomas of the pia mater" were independent of each other, and that both were caused by a profound systemic disorder akin to that of tuberous sclerosis.

GEORGE B. HASSIN.

HISTOPATHOLOGY OF THE EXTERNAL GENICULATE BODY. ALBERT T. STEEGMANN, Arch. Neurol. & Psychiat. **32**:763, 1934.

Using a variety of staining methods, Steegmann studied the condition of the external geniculate body in 141 persons who died of infectious, degenerative and toxic conditions, and contrasted the observations with those in 8 normal persons and 7 persons with schizophrenia. Of the usual changes in the ganglion cells, pigmentary atrophy was particularly common. It was also present in cases of uremia and epilepsy, though the cell changes were not of the "ischemic" type seen in Sommer's sector of the cornu ammonis. In general, the geniculate ganglion is not as sensitive to changes post mortem as other parts of the central nervous system.

GEORGE B. HASSIN.

HERNIATION OF THE NUCLEUS PULPOSUS: A CAUSE OF COMPRESSION OF THE SPINAL CORD. M. M. PEET and D. H. ECHOLS, Arch. Neurol. & Psychiat. **32**:924, 1934.

Peet and Echols report two cases in which there were symptoms of tumor of the spinal cord—in one case, of the cervical and in the other, of the lumbar region. In both cases laminectomy revealed herniation of the nucleus pulposus. The nucleus pulposus is an incompressible semigelatinous mass which may escape from the intervertebral disk under abnormal conditions, such as trauma and may then be mistaken for chordoma.

GEORGE B. HASSIN.

GLOMERULAR CHANGES IN NEPHRITIS. W. G. MACCALLUM, Bull. Johns Hopkins Hosp. **55**:416, 1934.

The structure of the capillary tuft of the glomerulus in the human body is unique. The capillaries stand in the same relation to the epithelium as those between the tubules do to the tubular epithelium, suggesting that the epithelium controls the function of the glomerulus. The basement membrane of the epithelium is separable from the wall of the capillary, and connective tissue exists in the glomerular tuft. Various injuries result in reparatory processes which produce

much new connective tissue between these capillaries, displacing them and compressing them. In some cases this is associated with great proliferation of the epithelium. In no case, however, has proliferation of the capillary endothelium been found to cause obstruction of the capillaries. Therefore, it would seem preferable to speak of intercapillary rather than intracapillary glomerulonephritis.

From the Author's Conclusions.

The Pathology of Amebiasis. H. E. Meleney, J. A. M. A. **103**:1213, 1934.

The lesions produced by Endamoeba histolytica are the result of its mechanical invasion of and toxic action on the tissues of the host. The toxic action is manifested by edema, fibrin formation, necrosis and dissolution in varying degrees, according to the types of tissue involved. In the colon, the mucosa is first attacked, but the submucosa suffers most severely, and the lesions may involve the deeper coats of the wall and result in perforation. There is little cellular reaction unless bacteria invade the lesions. Occasionally mild lesions are found in which amebas have invaded the mucosa and submucosa without producing definite necrosis. Partial or complete healing often takes place, and scar formation may lead to serious functional disturbances.

Hepatic abscesses secondary to intestinal lesions are a common complication. Sometimes these abscesses are small and multiple, but more often they are large and single and situated in the right lobe. Extension of the hepatic abscess through the diaphragm into the lung is common, with development of a secondary abscess of the lung surrounded by pneumonia. Extension into the pleural and pericardial cavities also occurs.

Amebic lesions of the intestine or liver may also extend into adjacent organs or tissues by direct contact. Amebic ulceration of the skin occasionally occurs following the drainage of visceral lesions or by direct extension through the anus from rectal ulcers. Amebic abscess of the brain is a rare though well recognized condition. The amebic etiology of other clinical conditions has not been established.

From the Author's Summary.

Staining of the Processes (Flagella) of Human Erythrocytes. W. W. Oliver, J. Infect. Dis. **55**:266, 1934.

The processes (flagella) on normal human red blood cells can be revealed in stained smears by employing a slightly altered Kulp modification of Löffler's method for staining bacterial flagella. The slight modifications which are suggested have resulted not only in a staining of the processes on human erythrocytes, but also in what seems to be an improvement in the staining of the flagella of bacteria.

From the Author's Summary.

Mesentericoparietal Hernia. J. J. Longacre, Surg., Gynec. & Obst. **59**:165, 1934.

The first concept as to the etiology of this form of hernia was that of Treitz, who thought that the hernia was caused by the pressure and peristaltic movement of the small bowel widening and deepening one of the many preformed fossae about the duodenojejunal flexure. Although these hernias were later discovered in new-born infants, the possibility of their interpretation on an embryologic basis was not considered until recently. Normally the colon grows across the abdomen superiorly and then down, thus avoiding imprisonment of the small bowel in its mesentery, but if rotation of the umbilical loop is reversed, the intestine is incarcerated behind the leaves of the colon's mesentery, and this forms most of the wall of the hernial sac. By careful dissection Longacre found that the site and the extent of the sac, the absence of a definite neck, the lack of omentum within the sac and, most important of all, the distortion of the blood supply to the colon justify the conclusion that mesentericoparietal hernia is a congenital anomaly rather than a postnatal development. To date 140 instances have been recorded in the literature.

From the Author's Summary [W. C. Hunter].

PEPTIC ULCER OF MECKEL'S DIVERTICULUM. L. B. JOHNSTON and G. RENNER, Surg., Gynec. & Obst. **59**:198, 1934.

Various reports indicate that gastric mucosa occurs in from 12 to 44 per cent of Meckel's diverticula. There are now on record forty-eight examples of peptic ulcer arising in diverticula possessing gastric mucosa either alone or in combination with mucosa of ileac or jejunal type or with pancreatic tissue. The condition is most frequently encountered in male infants and children. The ulcer is commonly single, is at the base of the diverticulum, extends into the ileac rather than into the gastric mucosa, and is usually of the chronic peptic type. Such ulcers may give rise to single or recurrent hemorrhages of severe degree or to perforation and peritonitis. In the group without perforation, intestinal hemorrhage is a most important clinical diagnostic point.

W. C. HUNTER.

HYDATID DISEASE OF THE BRAIN. HAROLD R. DEW, Surg., Gynec. & Obst. **59**:321, 1934.

Even in countries like Australia and the Argentine Republic, where hydatid disease is relatively common, primary cerebral hydatid cysts are rare. Statistics show that such cysts are seven times as frequently met with in the child as in the adult, owing to the fact that childhood is the period of poor personal hygiene and close contact with dogs. There seems to be no doubt that the peripheral distribution of hydatid disease is entirely dependent on the vagaries of the systemic arterial circulation, and the more frequent occurrence of cerebral cysts in children is explained by the comparatively large size of the carotid vessels in the child, which allows many embryos to be carried to the brain. Primary cysts are almost always single, and the frontal lobe of the cerebrum is the favorite site. The cysts often attain a considerable size but do surprisingly little damage to the brain tissue. The skull may be eroded, or there may be rupture into a lateral ventricle, in which event there are profound anaphylactic symptoms and usually death. Three cases are reported, all of the primary type, and one is of unusual interest because it occurred in an adult. Primary cysts of the adult brain are uncommon because the embryos have to make their way through the capillary beds of the liver and lung, after which only a small percentage can enter the carotid arteries, owing to the manner in which these arise from the relatively much larger aorta. In the adult, secondary and multiple cysts are to be anticipated and are the result of blood stream dissemination of scolices derived from a fertile primary cyst that has ruptured into the left side of the heart. The two types of hydatid cyst are different, but this has not been universally recognized, and the result has been a confusion in interpretation. The primary cyst is amenable to surgical treatment, while the metastatic form is not.

W. C. HUNTER.

Microbiology and Parasitology

VIRULENCE OF INFLUENZA BACILLI. L. HOYLE, J. Path. & Bact. **39**:681, 1934.

The virulence of many strains of influenza bacilli can be raised and the enhancement maintained indefinitely by intrapleural passage in rabbits. By intrapleural injection of cultures of influenza bacilli of raised virulence into rabbits bronchopneumonia can be consistently produced, the lesions having a close resemblance to those of human influenzal pneumonia. The results of intratracheal inoculation of influenza bacilli into rabbits and guinea-pigs suggest that it is probably not possible to produce a spreading tracheal infection in these animals, and although occasional animals so inoculated may die of septicemia or of bronchopneumonia, it is probable that severe traumatic damage to the lung is essential before such a result can occur. It is shown that a condition of hemorrhagic edema of the lungs readily develops in rabbits and guinea-pigs as a result of the introduction of liquids intratracheally, so that great caution is necessary in interpreting the significance of pulmonary lesions consequent on such inoculations.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTAL YELLOW FEVER IN MICE AND GUINEA-PIGS. G. J. STEFANOPOULO, Ann. Inst. Pasteur. **52**:553, 1934.

Stefanopoulo confirmed the work of others in successfully transmitting the virus of yellow fever to both laboratory and wild mice, the effects on which were similar. In animals intraperitoneally inoculated, greater amounts of virus were found in the brain than in the blood stream. The serum of survivors neutralized the virus; weak serums delayed paralysis or death. By intracerebral inoculation attempts were made to adapt several strains to rabbits, guinea-pigs and rats. Rabbits and rats proved refractory, although a third passage was reached with the latter. Transfers to guinea-pigs were successful, especially with strains well adapted to mice. The animals died regularly in eight or nine days with encephalomyelitis. Fatty degeneration of the liver was frequent. The source of the strain, however, as well as the method of its perpetuation and its age, may determine whether the virus will exhibit well defined neurotropic or will show enterotropic qualities. These factors must be considered in dealing with the choice of procedure in human immunization.

FROM THE AUTHOR'S CONCLUSIONS.

EXPERIMENTAL TRANSMISSION OF SYPHILIS TO THE BOVINE SPECIES. ANTOINE BÉCLÈRE, Ann. Inst. Pasteur **53**:23, 1934.

Inoculation of the Truffi strain of spirochetes into the genital tracts of calves by various procedures was followed, in three of four weeks, by the appearance of small papules containing spirochetes. Transfers were made directly from human beings, although the adaptation was accomplished with greater difficulty.

M. S. MARSHALL.

RABIES VIRUS IN THE LUNG. P. REMLINGER and J. BAILLY, Ann. Inst. Pasteur **53**:43, 1934.

Various strains of rabies virus were tested on rabbits, dogs, cats and guinea-pigs. Transfers from these infected animals in the acute stages of their infection indicated that the virus was present in the lungs in nine of twenty-four cases. The kidney, spleen and liver also contained the virus in nearly one third of the experiments.

M. S. MARSHALL.

INFECTION OF RABBITS VIA THE SUBARACHNOID ROUTE. P. ZDRODOWSKI and H. GOLINEWITCH, Ann. Inst. Pasteur **53**:120, 1934.

Meningococci introduced into rabbits by the subarachnoid route induced a fatal infection fairly constantly in those weighing 1.5 Kg. Rabbits were somewhat more susceptible than monkeys or dogs, although the course of their disease was similar to that in the latter. Therapeutic serum was effective under proper conditions, and tests of potency, based on protection, appeared to reveal inefficient serum and to furnish a measure of weakly, moderately or satisfactorily potent serum. Fresh virulent undissociated strains were needed for the production of good serum. These serums seemed to function chiefly through stimulation of phagocytic action.

In the same manner, Pfeiffer's bacillus from the spinal fluid of infants with meningitis was proved infective, was standardized and was used in the preparation of serum which could be tested for potency on rabbits. Streptococci and pneumococci were submitted to similar tests with some success but, rather more than with meningococcus and Pfeiffer's bacillus, instability of infectivity resulted in some difficulties.

M. S. MARSHALL.

DYSENTERY IN DENMARK. KNUD BOJLÉN, Comm. Inst. serothérap. de l'Etat danois, Copenhagen **24**:1, 1934.

The work deals with the bacteriology and epidemiology of the Sonne and Flexner bacilli which were responsible for all but 3 cases of dysentery in Denmark during the years 1926 to 1933. Three cases which were due to the Shiga-Kruse

bacilli were imported from outside Denmark. The Sonne dysentery bacilli were isolated from 751 patients and the Flexner bacilli from 247 patients. The bacilli were isolated partly in sporadic cases and epidemics of dysentery all over Denmark and partly in an endemic case in an asylum for the feebleminded. Bojlén employs a classification of dysentery bacilli into four groups (I. Shiga-Kruse, II. Flexner, III. Sonne and IV. Schmitz). This classification is made possible by the fermentation reactions with mannite, lactose and dulcite. A finer classification within each group is possible only by means of serologic reactions. In the group of the Sonne bacilli, the capacity or the incapacity to ferment xylose proved constant, while the ability to ferment maltose was subject to change in the course of time. The employment of various sugars permitted a separation into six biochemically well defined types. The Flexner strains could be divided into ten biochemically constant types, the ability of which to ferment sorbite and saccharose was stable; the others showed changes in the course of artificial cultivation. Before the work of Bojlén was undertaken, the clinical as well as the bacteriologic diagnosis of dysentery in Denmark was a rare thing. The epidemiologic result of his work has been to show that dysentery is a common infectious disease in Denmark. In about 2.7 per cent of the cases, chronic colitis develops. The results of sanitary measures in combating the disease in closed institutions and among the general population are extremely illuminating. The work includes a clear and exhaustive historical review of the development of knowledge of the bacteriology of the dysentery bacilli and of the epidemiology of dysentery, with a lengthy bibliography.

I. DAVIDSOHN.

UNUSUAL FORM OF TUBERCULOSIS OF THE STOMACH AND LIVER. S. GENKIN and J. SOSNOWIK, Virchows Arch. f. path. Anat. **292**:315, 1934.

A man, aged 22 years, had suffered for five years from a chronic progressive illness characterized clinically by abdominal and gastric pain, fever, progressive loss of weight and strength, diarrhea and secondary anemia. The clinical diagnosis was tuberculous peritonitis, perigastritis, periduodenitis and pancreatitis. At necropsy there was found an older tuberculous focus in the lung, and the clinical diagnosis of tuberculous involvement of the peritoneum was confirmed. In the report chief attention is paid to the tuberculous process in the liver and stomach. The latter organ and the duodenum were united to the inferior surface of the liver by tuberculous granulation tissue. From the latter, multiple tuberculous fistulas penetrated the wall of the stomach. Others communicated with tuberculous abscesses of the liver. The formation of these fistulas is ascribed to arterial thromboses in the tuberculous adhesions, resulting from narrowing of the vessels by contraction of the granulation tissue. The thromboses led to infarction along the course of the vessels and extension of the tuberculous process along these paths. The primary condition was tuberculosis of the lung. This led to tuberculous peritonitis, and this in turn, by direct continuity, to involvement of the stomach and liver.

O. T. SCHULTZ.

SEPSIS WITH ALLERGIC MANIFESTATIONS. G. MEYER-DÖRKEN, Virchows Arch. f. path. Anat. **292**:374, 1934.

Infection of the upper respiratory tract in a young man aged 19 years was followed by a protracted lung involvement of the type of a creeping pneumonia. The illness lasted half a year. Organisms were never cultivated from the blood. There was persistent eosinophilia, which reached a maximum of 77 per cent. This, together with attacks of erythema multiforme near the end of the illness, is held to have been an allergic reaction. Necropsy revealed pancarditis. Histologically there were changes in the arteries of the liver, kidney and other organs suggestive of periarteritis nodosa, but there was more marked productive inflammatory reaction of the intima than in periarteritis. There were small granulomatous lesions of the pleura and of the tissues of the neck like those of rheumatic infection, although no typical Aschoff bodies were found. The cardiac valvular lesions were like those of rheumatism. The granulomatous lesions of the myocardium and lung

contained many eosinophils. Accepting the allergic character of rheumatic lesions, the author interprets the case as one of sepsis with involvement of the tissues of the neck and with allergic reactions that manifested themselves as lesions simulating in part those of rheumatism and in part those of periarteritis nodosa.

O. T. SCHULTZ.

LOCAL ION EFFECTS ON TISSUES AND ON THEIR SUSCEPTIBILITY TO VIRUS. IRMENGARD SICHERT-MODROW, Virchows Arch. f. path. Anat. **292**:384, 1934.

Solutions of a variety of inorganic salts with an osmotic pressure equal to that of 0.6 per cent sodium chloride solution were injected subconjunctivally, subcutaneously and intramuscularly into rabbits and guinea-pigs. The degree of the local reaction was determined by the edema, hyperemia and time of resorption as noted grossly and by the tissue and vascular reaction as observed histologically. Resorption of bivalent and polyvalent ions was slower than that of univalent ions. When the injections were repeated at short intervals, the reaction was increased. With longer intervals, the reinjection was followed by less local reaction if the inflammatory reaction set up by the previous injection had completely subsided. The local susceptibility to the virus of foot and mouth disease was likewise increased if the interval between the injections of the salt solutions was short, and was decreased if the injections were so spaced that the inflammatory reaction caused by a previous injection had completely disappeared. Too strong a dose of virus broke down this locally increased resistance.

O. T. SCHULTZ.

ACTION OF BACTERIAL FILTRATES ON ENDOTHELIUM. K. APITZ, Virchows Arch. f. path. Anat. **293**:1, 1934.

A series of rabbits received intravenous injections of variable quantities of a bacteria-free filtrate of a broth culture of colon bacilli. The animals were killed at varying intervals and their tissues subjected to microscopic examination. The most striking change noted was hemorrhagic inflammation at the site of injection; the internal organs revealed slight parenchymatous degenerative changes. In a second series of rabbits the first injection was followed on the next day by one or several injections of the same filtrate. In these animals there were observed fibrinous thrombi of the small blood vessels and multiple hemorrhages. The latter were most extensive in the kidneys but were present also in other organs. The first injection, according to Apitz, causes an alteration of the cellular protoplasm, especially of that of the vascular endothelium, which renders it more highly susceptible to further injections of the same toxic material. This reaction is a generalized Shwartzman phenomenon. It is distinct from the allergic reaction, in that it is not due to an antigen-antibody reaction but to a nonspecific alteration of protoplasm that renders it immediately hypersusceptible to the action of toxic agents.

O. T. SCHULTZ.

MIXED INFECTION IN THE WALLS OF TUBERCULOUS CAVITIES IN THE LUNGS. MAX KASPER, Zentralbl. f. Bakt. (Abt. 1) **126**:252, 1932.

Kasper gives a good review of the literature on the problem of mixed infection of tuberculous cavities and describes his experiments in which sections through the walls of cavities in thirty-three patients were studied. Gram stains were made in all instances. Contrary to the previous observations, bacteria were not found deep in the walls of the cavities except in a few instances. Some appeared to be gram-negative cocci; others were gram-positive diplococci, and these occurred principally around blood vessels and with no especial inflammatory reaction near them.

PAUL R. CANNON.

STREPTOCOCCI IN WHITE MICE. HANS GROSSMANN, Zentralbl. f. Bakt. (Abt. 1) **127**:225, 1933.

With rigid aseptic precautions, Grossmann made a study of the germ content of the blood and organs of healthy white mice. Streptococci were found frequently

in the lungs, liver, spleen, kidneys, lymph nodes and peritoneal cavity. The majority of the strains belonged to the type Streptococcus lacticus, but some resembled Streptococcus pyogenes. Exposure of mice to intensive ultraviolet radiation had no influence on the streptococcus content of organs.

PAUL R. CANNON.

THE CULTIVATION OF VACCINE VIRUS IN VITRO. F. BREINL, Zentralbl. f. Bakteriol. (Abt. 1) **127**:308, 1933.

A strain of vaccine virus was cultivated in Maitland's medium through a long series of passages. Less active multiplication was obtained when rabbit kidney, guinea-pig testis or guinea-pig kidney was used. Rabbit spleen or urine, plant tissues and yeast cells were useless. The growth-promoting substance was destroyed by heating at 45 C. for thirty minutes. The virus grew best in a range of p_H of from 6 to 9.2. It did not grow when deprived of oxygen.

PAUL R. CANNON.

EXPERIMENTS ON ELEVATION OF THE VIRULENCE OF B C G. F. GERLACH, SILVIO SEGRE and J. BROSCH, Zentralbl. f. Bakt. (Abt. 1) **127**:312, 1933.

Cultures of B C G were observed under certain conditions to see whether an increase in virulence resulted. B C G 8 was grown deep in veal glycerol broth for four months, and the cultures were then inoculated subcutaneously or intraperitoneally into guinea-pigs in doses of from 1 to 2 mg. The lesions which resulted differed in no way from those produced by injecting surface broth cultures of the same strain. Cultures grown in the depths of fluid mediums or in mediums reinforced with rabbit serum showed no increase in virulence for rabbits. Prolonged cultivation in the depths of these mediums frequently led to a diminution in virulence but in no instance to an increase in virulence.

PAUL R. CANNON.

SUSCEPTIBILITY OF FOWL TO BACTERIA OF THE BRUCELLA GROUP. K. BELLER and W. STOCKMAYER, Zentralbl. f. Bakt. (Abt. 1) **127**:456, 1933.

Bacteria of the Brucella group of bovine and porcine origin were used in an attempt to determine the susceptibility of young hens. The latter were susceptible to large doses of cultures injected intravenously or intramuscularly, less so to cultures injected intraperitoneally. They were practically insusceptible to organisms that were fed. The symptoms in the infected animals were slight and disappeared quickly. On the fourth day after injection agglutinins appeared. They were strongest after parenteral injection, less so after cutaneous application of living cultures and least so after peroral administration. The micro-organisms persisted longest in the spleen and bone marrow. The different types of micro-organisms used showed no difference in pathogenicity.

PAUL R. CANNON.

DEMONSTRATION OF TUBERCLE BACILLI IN THE BLOOD. HAROLD LOTZE, Zentralbl. f. Bakt. (Abt. 1) **127**:481, 1933.

Blood from twenty patients was cultured by Löwenstein's method in an attempt to test the latter's claim that tubercle bacilli can be recovered readily from the blood of such patients. Tubercle bacilli were not isolated in any instance. The reasons for the discrepancy in the findings are discussed.

PAUL R. CANNON.

THE RELATION BETWEEN HEMOLYSIS AND THE BLOOD GROUPS. H. ELBEL and F. J. HOLZER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:175, 1934.

The hemolytic action of saponin, of hypotonic solutions of sodium chloride and of normal ox serum on human red blood corpuscles of the four classic groups and of the M, N and MN groups was studied. No differences were observed which had any relation to the blood groups.

I. DAVIDSOHN.

THE ANTAGONISTIC ACTION OF COLON BACILLI. ITALO RIZZI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:380, 1934.

The antagonism of colon bacilli against anthrax bacilli was greater than, though in principle similar to, that against typhoid bacilli. The antagonistic action was weak in strains obtained from infants, from old persons with arthritis deformans or with constipation, from patients with noninfectious enteritis and from schizophrenic patients. Active strains of colon bacilli destroyed easily very large numbers of anthrax bacilli.

I. DAVIDSOHN.

TWO ATTACKS OF POLIOMYELITIS AT AN INTERVAL OF TWENTY-FOUR YEARS. M. TESDAL, Norsk mag. f. lægevidensk. **95**:978, 1934.

The literature contains at least twelve instances of a second attack of poliomyelitis. In Tesdal's instance the first attack occurred at the age of 16 years, when both legs became paralyzed, and the second at the age of 40 years, when both arms became paralyzed.

INFECTION WITH STREPTOCOCCUS EPIDEMICUS. TH. THJØTTA and S. D. HENDRIKSEN, Norsk mag. f. lægevidensk. **95**:1361, 1934.

In a series of infections in Oslo, Norway, a capsulated streptococcus was found which formed mucoid colonies and which corresponded closely to Streptococcus epidemicus as described by Davis and Rosenow in 1912 in the Chicago epidemic of septic sore throat. Serologically the stains formed two groups, a larger one from cases in Oslo and the vicinity and one of three strains from cases farther north, but the difference was not marked enough to indicate two different types.

Immunology

THE ANTIBODY RESPONSE OF RABBITS TO HOMOLOGOUS BRAIN. F. F. SCHWENTKER and T. M. RIVERS, J. Exper. Med. **60**:559, 1934.

Rabbits given injections of fresh emulsions of homologous brain acquired few or no antibodies capable of fixing complement in the presence of aqueous emulsions or alcoholic extracts of rabbit brain. Complement-fixing antibodies, however, were produced in rabbits by means of injections (1) of sterile emulsions of homologous brain which had been allowed to stand at room temperature for from five to thirty days and (2) of emulsions of homologous brain experimentally infected with vaccine virus. The antiserums that were produced following injections of emulsions of autolyzed homologous brain were shown by absorption tests to contain both specific and nonspecific antibodies. The specific brain antigen was found to be approximately six times as abundant in the white as in the gray matter. It was almost absent from the brain of fetal and newly born rabbits, but increased in amount with the age of the animal to reach a maximum concentration at maturity. The specific antigen seemed to parallel the myelin content of brain tissue.

FROM THE AUTHORS' SUMMARY.

THERMOPRECIPITATION IN TRYPANOSOMA EQUIPERDUM INFECTION. H. A. POINDEXTER, J. Exper. Med. **60**:575, 1934.

There is a heat-resistant precipitable substance in extracts of the spleens of rats, guinea-pigs and rabbits infected with T. equiperdum. It does not appear to be within the body of the trypanosome itself. Antibodies to this substance are found in the serum of infected animals. The antibody strength of the serum of rats seems to be relatively less than that of the other animals, but the power of extracts from the spleens of infected rats appears to be equivalent to that of similar extracts from the spleens of the other animals. The antibody titer of the serum of rabbits was greater than that of the other two species investigated.

This was shown not only by the reaction with the extracts of spleens of the same species, but also by that with extracts of the spleens of similarly infected animals of other species.

FROM THE AUTHOR'S SUMMARY.

CHEMICAL STUDIES ON BACTERIAL AGGLUTINATION. M. HEIDELBERGER and E. A. KABAT, J. Exper. Med. **60**:655, 1934.

A method, conforming to the criteria of quantitative analytic chemistry, is described for the estimation of the agglutinin content of antiserums. Examples are given of the application of the method to various antipneumococcus serums. This new, absolute method is discussed with regard to its relation to the commonly used relative methods.

FROM THE AUTHORS' SUMMARY.

CORTIN PROTECTION AGAINST ANAPHYLACTIC SHOCK IN GUINEA PIGS. J. WOLFRAM and R. L. ZWEMER, J. Exper. Med. **61**:9, 1935.

Studies have been made on a possible protective action of cortin in the prevention of anaphylactic shock induced by crystallized egg. Of sixteen control guinea-pigs, only two survived. Sixteen of thirty-three cortin-treated animals received the hormone at the optimum period of from two to six hours before the shocking dose. Nine survived, and two others showed some protection. In groups treated at other intervals of time the evidence of protection was inconclusive. Two weeks after the first test the cortin-treated survivors succumbed to a second dose of antigen, which was not preceded by cortical extract.

FROM THE AUTHORS' SUMMARY.

THE RATE OF ANTIBODY FORMATION IN MONKEYS IMMUNIZED WITH POLIOMYELITIS VIRUS. M. BRODIE, J. Immunol. **27**:395, 1934.

A single subinfective intracutaneous inoculation of spinal cord containing active poliomyelitis virus gives rise to an immunity which appears at or soon after the sixth day and reaches its height by the twentieth day. The immunity lasts for a considerable time, being still present a year later. A second dose of antigen gives rise to considerable additional immunity if it is administered during the rise or height of the antibody response to the first; but it is not nearly so effective if given during the lag phase of the first inoculation. The second dose of antigen does not interfere with the effects of the first, and it acts more rapidly than the first. Two doses of active spinal cord given at ten to twenty day intervals give rise to a higher degree of immunity than exists after mild or severe forms of the disease.

FROM THE AUTHOR'S SUMMARY.

AGE AND ANTIBODY PRODUCTION. L. BAUMGARTNER, J. Immunol. **27**:407 and 417, 1934.

Studies with antiserums produced by animals of different ages indicate that there are qualitative and quantitative differences in each serum which are associated with the age of the animal elaborating it. These experiments also corroborate the view that serums of the same titer may each have qualitative characteristics which are independent of the titer and which allow two given serums of the same titer to react differently.

FROM THE AUTHOR'S CONCLUSIONS.

THE AGGLUTINOGENS M AND N OF LANDSTEINER AND LEVINE. A. S. WIENER, R. ZINSHER and J. SELKOWE, J. Immunol. **27**:431, 1934.

The most important requirement for accurate results is proper potent reagents. For the preparation of potent serums, prolonged and intensive immunization is necessary, and when preparing anti-M serums the desired effect is often obtained by giving the rabbits a long rest period (one or more months) followed by an additional brief course of injections. The preparation of the anti-N testing fluid from the immune serum offers more difficulty than the preparation of anti-M fluid,

because of the greater tendency to nonspecific absorption with the former. However, there is usually no difficulty in preparing fluids with a titer of at least from 10 to 20, and with reagents of such potency accurate results are possible. The majority of bloods of the heterozygous type are less sensitive to agglutination than bloods of the corresponding homozygous types, so that it is important to include an adequate number of control bloods of each of the three types M, N and MN in every experiment. Other factors which must be taken into account are the possible presence of interfering agglutinins, which can be removed by suitable absorption experiments, and the effect of variations in the concentration of the suspension, the age of the blood and the temperature. In medicolegal cases, absolute reliance should not be placed on any single set of reagents; for such work adequate experience is of prime importance.

From the Authors' Summary.

Rapid Agglutination Test for Infectious Abortion in Cattle. C. R. Donham and C. P. Fitch, J. Infect. Dis. **55**:60, 1934.

Washing Brucella abortus organisms for use in rapid-test preparations of antigen with phenolized saline solution resulted in slightly more sensitive antigens than were obtained when unwashed bacteria were used. Serums which exhibit "pro-agglutinoid" zones by the test tube method usually do not show such reactions when tested by the rapid method. This is further evidence that the two methods of testing are dependent on different elements of activity. Significant variations in the sensitivity of rapid-test antigens made from different strains of the organism were encountered. The sensitivity of successive preparations of the antigen made from a single strain of the organism may vary. Polyvalent preparations of rapid-test antigen seem preferable. The problem of "slow agglutination" of rapid-test antigen has not been solved by the method of preparing such antigen, as has been described in the literature. Two to three minutes is too short a time to make the final observations of the results of rapid agglutination tests with antigen preparations now available.

From the Authors' Summary.

Active Immunization Against Tetanus with Tetanus Toxoid. D. H. Bergey, J. Infect. Dis. **55**:72, 1934.

Alum-precipitated tetanus toxoid, in a dose of 1 cc., induces a higher degree of immunity than three doses of the toxoid without alum. The tetanus toxoid is of value only as a prophylactic agent. It has no therapeutic value in persons who are infected with tetanus bacilli. Active immunization against tetanus infection should be carried out as follows: A primary stimulus is given by injecting a dose of 1 cc. of the toxoid; this is followed by a period of rest of three months, and then a secondary stimulus is given by injecting another dose of 1 cc. of toxoid. On injury, a third dose of 1 cc. of the toxoid is given.

From the Author's Conclusions.

Study of Vaccinal Immunity by Means of Complement Fixation. R. F. Parker, J. Infect. Dis. **55**:88, 1934.

In experimental vaccinia the development of specific complement-fixing bodies for the virus of vaccinia is associated with the development of virus-neutralizing antibodies. In rabbits, the complement-fixing antibodies gradually disappear and are usually no longer demonstrable from twelve to fourteen months after vaccination. With the data at hand, the cutaneous response of the rabbit cannot be predicted by the complement-fixing activity of the serum. On reinfection there is a prompt and rapid rise of the titer of complement-fixing bodies without apparent relation to the intensity of the cutaneous reaction. In man positive complement fixation is demonstrable in many cases after vaccination, the incidence being apparently related to the severity of the local reaction.

From the Author's Conclusions.

ANTIGENIC RELATION OF GRAVIS STRAINS OF DIPHTHERIA BACILLI AS COMPARED WITH PARK 8 STRAIN. S. ETRIS, J. Infect. Dis. **55**:220, 1934.

Park 8 antitoxin in sufficient doses will neutralize the toxin of the gravis group and protect guinea-pigs against a fatal dose of gravis culture. The tests, however, have brought out a quantitative difference in the neutralization of the gravis toxin by Park 8 antitoxin and a greater specific protective value of the gravis antitoxins against living gravis organisms. The London gravis strain falls into a type serologically different from that of the other strains used in this study, corroborating the work of Ewing in typing this particular strain.

FROM THE AUTHOR'S SUMMARY.

PRECIPITINOGENIC ACTION OF HUMAN PLASMA AND ITS CONSTITUENTS. L. HEKTOEN and W. H. WELKER, J. Infect Dis. **55**:271, 1934.

The intramuscular injection of human plasma or human serum, especially when absorbed by aluminum hydroxide, results in a production of specific precipitins which may be continued for months. The precipitin reaction of human plasma or serum appears to result from the single or conjoint action of individual specific precipitins against the various antigens in the plasma or serum.

FROM THE AUTHORS' SUMMARY.

IMMUNITY TO THE ST. LOUIS TYPE OF ENCEPHALITIS. J. G. WOOLEY, Pub. Health Rep. **49**:1495, 1934.

The serum protection tests reported here indicate that the St. Louis type of encephalitis (1933) is immunologically distinct from encephalitis lethargica, poliomyelitis and the postinfection encephalitides.

FROM THE AUTHOR'S SUMMARY.

THE ENVELOPE ANTIGEN OF B. PESTIS AND ITS ANTIBODY. H. SCHÜTZE, Brit. J. Exper. Path. **15**:200, 1934.

The examination of three antiplague serums has demonstrated that envelop antibody is contained chiefly in the pseudoglobulin fraction of buffalo serum and in the euglobulin fraction of sheep serum. The protective values of such serums against a simultaneous subcutaneous dose of living Bacillus pestis are correlated with their contents of envelop antibody as recorded by the precipitin test. The envelop antigen of B. pestis readily suffers damage by heat. After being heated to 70 C. for thirty minutes it retains but little power of producing antibodies in rabbits, while it is completely haptenized by being heated to 80 C. for fifteen minutes. The sensitiveness of this antigen to alkali is indicated by its complete destruction by eighth-normal sodium hydroxide acting for an hour at 60 C. Eighth-normal acetic acid achieves the same result after fifteen minutes at 100 C. Plague vaccine, whether grown in broth or in agar, generally has a p_H of over 8. Sterilization of the vaccine by heating it to 56 C. at this reaction reduces its power of evoking precipitins in rabbits, but such damage may be prevented by neutralizing the vaccine before sterilization. It is suggested that this sensitivity of envelop antigen to alkali may be of importance in the production of prophylactic antiplague vaccines.

FROM THE AUTHOR'S SUMMARY.

THE PURIFICATION OF TUBERCULIN. G. A. C. GOUGH, Brit. J. Exper. Path. **15**: 237, 1934.

A rapid method of obtaining a highly active tuberculin preparation by adsorption on benzoic acid is described. The cutaneous activity of old tuberculin has been shown to be associated with two fractions, viz., typical proteins and a proteose-like substance which is not precipitated with trichloracetic acid. The molecular sizes of the different active products are compared by ultrafiltration.

FROM THE AUTHOR'S SUMMARY.

TYPE-SPECIFIC AND GROUP-SPECIFIC SERA AGAINST STREPTOCOCCI. H. LOEWENTHAL, Brit. J. Exper. Path. **15**:298, 1934.

Strains of hemolytic streptococci may exhibit different forms of colonies, which differ widely in their serologic reactions. The N form is highly specific, as shown by agglutination with absorbed antiserum and by protection test in mice. The protective value of its antiserum, therefore, is limited to the homologous form. There are two less specific O forms: (*a*) capsulated and (*b*) noncapsulated. The agglutination, precipitation and capsular swelling reactions of the former correspond to the carbohydrate nature of its capsular substance. Preparation of highly efficient antiserum is possible. All strains of the capsulated form seem to belong to one serologic type. The noncapsulated O form is more frequent. Agglutination tests as well as protection tests indicate that there are several serologic types of this form. Cross-protection can be obtained between organisms of the same type. Both O and N forms can be virulent, and both forms may occur in the primary culture from disease.

FROM THE AUTHOR'S SUMMARY.

THE ELEMENTARY BODIES OF ZOSTER AND THEIR SEROLOGICAL RELATIONSHIP TO THOSE OF VARICELLA. C. R. AMIES, Brit. J. Exper. Path. **15**:314, 1934.

Elementary bodies morphologically similar to those found in varicella and vaccinia are constantly present in the vesicle fluid of zoster. Pure suspensions of these bodies, prepared by high speed centrifugation of zoster vesicle fluid, are specifically agglutinated by zoster convalescent serum. Attempts to demonstrate a relationship of zoster and varicella by means of cross-agglutination tests have met with a fair measure of success.

FROM THE AUTHOR'S SUMMARY.

BACTERIAL HAEMOLYSINS. E. W. TODD, J. Path. & Bact. **39**:299, 1934.

Hemolytic streptococci from human infections produce an antigenic streptolysin which is serologically group-specific but not type-specific; in addition to this antigenic streptolysin, which is subject to reversible oxidation and reduction, they also produce another variety of streptolysin which is not subject to reversible oxidation and reduction and which appears to have no antigenic activity. The streptolysins of hemolytic streptococci from animal infections do not appear to be antigens, and they are not subject to reversible oxidation and reduction. Soluble streptolysin prepared from "pseudohemolytic" streptococci appears to be nonantigenic. Lancefield's groups of hemolytic streptococci each produce different varieties of streptolysin which may be distinguished from one another by their reactions to oxygen, to heat and to acid. Serums with a high titer of antistreptolysin from hyperimmunized horses neutralize tetanolysin and pneumococcic hemolysin to a limited extent; the degree of neutralization is not necessarily correlated with the titer of antistreptolysin, and the different hemolysins are distinguishable by quantitative serologic methods. This partial antigenic overlapping of hemolysins can de demonstrated only by the use of hyperimmune serums; it is not seen when the comparatively low-titered antistreptolysin serums of patients infected with hemolytic streptococci are examined, and it therefore does not interfere with the use of antistreptolysin titers for the diagnosis of streptococcic infections. The hemolysin of staphylococci is not serologically related to streptolysin.

FROM THE AUTHOR'S SUMMARY.

IMMUNISATION OF MICE AGAINST RIFT VALLEY FEVER. R. D. MACKENZIE, J. Path. & Bact. **40**:65, 1935.

Mice have been successfully immunized against Rift Valley fever by means of a vaccine prepared according to the method of Perdrau and Todd or by the use of dilute solution of formaldehyde. The vaccine was equally efficient whichever method was used. The efficiency of the vaccine was in direct proportion to its

concentration. Within the limits of the experiment, variation in the size of the infecting dose was without effect. The failure of the earlier attempts at immunization was due to weakness of the antigen.

FROM THE AUTHOR'S CONCLUSIONS.

PROTEINS OF THE TUBERCLE BACILLUS. W. SCHAEFER and G. SANDOR, Ann. Inst. Pasteur **53**:72, 1934.

Lipoid substance extract from cultures of the tubercle bacillus induced the formation of antibodies which reacted only with the protein substance, and antibodies resulting from injection of the protein reacted only with the lipoid antigen. Organisms treated with fat solvent absorbed antiprotein antibodies completely, but only partially removed antilipoid antibodies. Organisms injected into horses and rabbits induced the formation of both types of antibodies, the antiprotein type appearing and disappearing sooner. Anti-B C G serum did not give unilateral absorption. Antiserum against tubercle bacilli of warm-blooded animals contained specific antibodies, not reacting with the reptile type nor with other acid-fast organisms tested. On the other hand, antiserum against the grass bacillus was less specific. Tuberculous human serum contains both protein and lipoid antibodies, and the use of both antigens in complement-fixation tests increases the number of positive results 25 per cent. The proportions of the two antibodies vary.

FROM THE AUTHORS' SUMMARY.

DEMENTIA PRAECOX AND TUBERCULOSIS. ADOLF BECK, Ann. Inst. Pasteur **53**:156, 1934.

Neither tuberculous antigens nor tuberculous antibodies were found in the spinal fluids of forty-two persons with dementia praecox. Of ten patients with tuberculous meningitis, only four had antibodies in the spinal fluid. The Vernes reaction was negative in all cases of dementia praecox and positive in all cases of tuberculous meningitis. Of sixty-five serums from patients with dementia praecox, 21.5 per cent showed tuberculous antibodies. In fifty serums from patients with other mental diseases, the tests were negative. The Vernes reaction was positive in 10.7 per cent of the former, and in none of the latter. Skin reactions with regular and special tuberculous antigens were positive in 96 per cent of patients with dementia praecox, and in 91.5 per cent of patients with other mental disorders; the reactions of the former group were often more marked. Thus no etiologic relation between tuberculosis and this mental disease was demonstrated.

FROM THE AUTHOR'S CONCLUSION.

ALLERGIC REACTIONS IN TUBERCULOSIS AND BRUCELLIASIS. W. SARNOWIEC, Ann. Inst. Pasteur **53**:166, 1934.

Thirty per cent of tuberculous guinea-pigs that had been inoculated three months previously reacted with abortin (bacterial bodies). Eighteen per cent reacted two months and 10 per cent one month after inoculation. Animals given injections of B C G, however, failed to respond to abortin. Animals infected with Brucella did not react to tuberculin. Although four human subjects with clinical tuberculosis failed to react to filtrate abortin, three responded to cellular abortin prepared by the author's method. Cows with Brucella infection responded, though weakly, to tuberculin.

M. S. MARSHALL.

THE ANTIGENS OF THE RED BLOOD CORPUSCLES. MADELEINE DUPONT, Arch. internat. de méd. expér. **9**:133, 1934.

The article contains a review of the more important contributions to the knowledge of the antigenic substances of human red blood corpuscles. Dupont adds to that knowledge the results of a study of the relationship between the antigenic substances in human blood cells and similar substances in the blood cells and tissues of various species of animals. Renal tissue from the guinea-pig

and to a lesser degree hepatic tissue from the rabbit were able to fix agglutinin α from human iso-agglutinating serum. Kidney tissues from the sheep, hog and ox had traces of such an antigenic property. The antigenic substances in the tissues of these animals are similar but not identical with the human blood quality A. On the other hand, the serums of the sheep, hog and ox contained anti-A agglutinins. The anti-A agglutinins were either of a specific variety, i. e., able to react exclusively with the true human blood group quality A, or of the so-called nonspecific variety, i. e., able to react with the antigenic substances in the animal tissue which are similar to the human quality A. Finally these serums may contain a mixture of the two. The red blood celis of the rabbit and to a slight degree also those of the ox, pig and guinea-pig were able to fix iso-agglutinin β from human serum. Such B-like properties were also found in various organs of guinea-pigs, rabbits and sheep, while organs of the ox and hog had only traces of it. The property N was found in the organs, but not in the red corpuscles, of some rabbits, guinea-pigs, oxen, pigs and sheep. The property M was absent in the red corpuscles, but present in the tissues, of some of the animals, but less frequently than the property N. The frequent and rather irregular presence of the M and N properties in the rabbit explains the difficulty that is encountered in the production of anti-M and anti-N immune serums. The wide distribution of the properties A and B in nature may explain the origin of the corresponding iso-agglutinins in man and in animals.

I. DAVIDSOHN.

ANAPHYLACTIC METABOLIC REACTION OF ISOLATED TISSUES. G. BOSTRÖM, Klin. Wchnschr. **13**:399, 1934.

Large amounts of specific antigen added to liver and skin from animals sensitized with horse or goat serum or ovalbumin decrease anaerobic glycolysis and respiration in these tissues, while small doses increase the metabolism. A similar effect on aerobic glycolysis in the liver was noted after the addition of the antigen. In tissues from nonsensitized animals, the antigens produced no reaction, or it occurred with much larger doses.

AUTHOR'S SUMMARY.

A SEROLOGIC TEST FOR GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS). HEINRICH LEHNDORFF, München. med. Wchnschr. **81**:447, 1934.

Lehndorff reviews the publications which deal with the presence of heterophilic antibodies in the serum of patients with infectious mononucleosis and concludes that the diagnostic importance of the test for heterophilic antibodies is similar to that of the Wassermann test: It is pathognomonic for the disease. A case is reported in which the reaction was very strongly positive.

I. DAVIDSOHN.

ORIGIN AND NATURE OF AMYLOIDOSIS. E. LETTERER, Virchows Arch. f. path. Anat. **293**:34, 1934.

After a rather full discussion of the problems in amyloidosis that still remain to be solved, Letterer presents the results of serologic investigations that substantiate his own and Loeschke's earlier independent observations that amyloidosis is the result of a local precipitation of altered homologous tissue proteins by isoprecipitins. His investigations lead him to conclude that amyloidosis is a disease characterized by a precipitating antigen-antibody reaction of organ tissues. The antigen is altered homologous protein, the formation of which is not restricted to leukocytes. The serum content of precipitating antibody for body protein is low in animals that have already developed amyloidosis, but is high in those that have been subjected to procedures which lead to amyloid infiltration but in which this state has not yet developed. Amyloidosis results when the antigen content of the blood is high and the precipitinogen content of the tissue fluids is low. Nutrition, through its influence on the formation of antibody, may prevent, delay or accelerate the deposition of amyloid. Atypical amyloidosis or paramyloidosis is the result of an altered antigen-antibody relationship.

O. T. SCHULTZ.

THE PROBLEM OF RAT-BITE HEMOLYSIN AND REAGIN. T. SANI and S. SANADA, Zentralbl. f. Bakt. (Abt. 1) **127**:426, 1933.

Rat-bite infection causes the development in the serum of "rat-bite hemolysins and reagins." The former are closely related to the Forssman antibody but differ in that the rabbit serum does not hemolyze cat blood and the thermolability is lower. The "rat-bite reagin" is similar to the "reagin" in syphilis and frambesia but differs in thermolability.

PAUL R. CANNON.

THE MÜLLER "BALL" PHENOMENON. R. MÜLLER and M. MANDULA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:183, 1934.

When increasing amounts of cholesterol are added to alcoholic extracts of heart tissue and subsequently physiologic solution of sodium chloride is added, two zones of maximum flocculation result, separated by a clear colloidal zone. The morphology of the floccules differs greatly in the two zones. Most of the flocculation tests (for instance, the Sachs-Georgi, the Kahn) are based on precipitation in the first zone, while the Müller test is based on that in the second zone. Similarly, two zones are observed when the quantity of physiologic solution of sodium chloride is progressively increased but only at a certain definite concentration of the cholesterol. The quantity of physiologic solution of sodium chloride which is used for the dilutions of the alcoholic heart extract and the length of time during which the diluted extract has to ripen to obtain the optimum "ball" effect after the serum has been added are proportionate to each other.

I. DAVIDSOHN.

Tumors

EFFECTS OF OESTRIN APPLIED TO SKIN OF MICE. HAROLD BURROWS and N. M. KENNAWAY, Am. J. Cancer **20**:48, 1934.

A solution of theelin prepared from the urine of pregnant mares and applied by brush to the nonepilated skin of the interscapular region in twenty male and ten female mice, induced accumulation of keratinized epithelium in the vagina, expansion of the uterine horns, hydronephrosis, atrophy of the testicles, diminution in the size of the seminal vesicles, enlargement of the posterior lobes of the prostate and distention of the prostatic alveoli with masses of keratin.

JACOB KLEIN.

ACTION OF SOME POLYCYCLIC AROMATIC HYDROCARBONS IN PRODUCING TUMOURS OF CONNECTIVE TISSUE. G. BARRY and J. W. COOK, Am. J. Cancer **20**:58, 1934.

Spindle cell tumors of connective tissue have been obtained in rats and mice by injecting fatty solutions of 1:2:5:6-di-benzanthracene, 5:6-cyclopenteno-1:2-benzanthracene and chrysene; a slight amount of neoplastic growth has been produced by the fatty medium (lard) alone. The tumor-like tissue obtained with lard showed none of the characteristics of malignancy. In experiments carried out with chrysene on the skin of 270 mice, of which 103 have lived for more than one year, no epitheliomas have been produced as yet. The same agents (1:2:5:6-di-benzanthracene and 5:6-cyclopenteno-1:2-benzanthracene) can produce sarcomas as well as carcinomas, but the order of activity of the two compounds does not seem to be the same for the two types of tumor. This applies both to rats and to mice.

AUTHORS' SUMMARY.

CHORDOMA OF THE CRANIUM AND CERVICAL PORTION OF THE SPINE. G. M. HASS, Arch. Neurol. & Psychiat. **32**:300, 1934.

After a discussion of chordoma in general, Hass describes a spheno-occipital chordoma in a man aged 59. The symptoms were those of bulbar paralysis and general weakness. The chordoma was situated in the posterior fossa of the skull,

projected from the floor anterior to the foramen magnum and extended to the upper part of the spinal cord. The predominating cells were physaliphorous, single or arranged in clusters. Many were vacuolated and contained mucin. Gelatinous or mucinous material made up the bulk of the tumor and was mixed with fragments of bone. Many areas of the tumor could not be distinguished from cartilage.

GEORGE B. HASSIN.

THE RELATION OF COLOR TO THE INCIDENCE OF MAMMARY TUMORS IN MICE. C. C. LITTLE, J. Exper. Med. **59**:229, 1934.

The facts recorded in this paper demonstrate that not all forms of tumors or all colors of mice can be lumped together in studying either the physiology or the genetics of the spontaneous incidence of tumors.

FROM THE AUTHOR'S SUMMARY AND CONCLUSIONS.

LYMPHOMATOSIS, MYELOMATOSIS AND ENDOTHELIOMA OF CHICKENS CAUSED BY A FILTERABLE AGENT. J. FURTH, J. Exper. Med. **59**:501, 1934.

When stimulated by a filtrable agent of leukosis of chickens (strain 2), endothelium may undergo seemingly unrestricted growth. These neoplasms of endothelium are usually unaccompanied by the formation of blood cells. Occasionally they produce hemocytoblasts, discharged like those of the normal marrow into vascular channels, also myelocytes about the vessels. The same agent that stimulates endothelium also stimulates erythroblasts, myelocytes and hemocytoblasts to unrestricted growth without obviously affecting the endothelium; and the association of endothelioma and leukosis is the result of stimulation of several types of cells by a single virus. Myelocytes appear also to develop from mesenchymal or endothelial cells without the intermediary stage of hemocytoblasts. It is often impossible to determine whether the neoplasms caused by the virus of strain 2 are of endothelial or mesenchymal origin, and it is possible that both types of cells may be stimulated by the same virus. Types of sarcoma like those described by Rous are not produced by the virus of strain 2.

FROM THE AUTHOR'S CONCLUSIONS.

OPERABILITY AND PROGNOSIS IN GASTRIC CARCINOMA. A. O. WHIPPLE and T. S. RAIFORD, Puerto Rico J. Pub. Health & Trop. Med. **9**:219, 1934.

Classifications of gastric carcinomas into pathologic types and grades are at best inexact. When combined with preoperative and operative findings, however, and studied from a critical standpoint, they should be helpful to the surgeon in determining the operability and operative procedure and to both the pathologist and surgeon in predicting the ultimate result.

There are two groups of carcinomas in which early diagnosis is especially difficult. One is the infiltrating type of growth appearing in a patient without previous gastro-intestinal symptoms, the first manifestation of illness being vague constitutional disorders. The second group includes those in patients with a history and positive diagnosis of chronic gastric ulcer, in which the insidious advent of malignant manifestations comes all too late to allow the satisfactory control of a highly malignant lesion.

It is the opinion of the authors that the best management of a disease with such disastrous consequences can be secured only through the medium of a combined clinic in which the physician, surgeon, roentgenologist and pathologist cooperate in establishing the diagnosis at the earliest possible stage of the disease. To do this they must become familiar with the history of the lesion, disregarding no salient feature from the first appearance of any untoward symptom until the resected growth has reached the pathologist.

AUTHORS' DISCUSSION.

BONE SARCOMA (OSTEOBLASTOMA). A. BRUNSCHWIG and P. H. HARMON, Surg., Gynec. & Obst. **57**:711, 1933.

Two cases in man, and one in an animal, of bone sarcoma are reported, and thirty-seven instances collected from the literature, in which there was ossification of both the primary tumor and the metastases in various tissues. No explanation accounts for these tumors except the one that they are malignant changes of osteoblasts or bone-forming cells. Thus they afford conclusive evidence for the existence of osteoblasts. The term "malignant osteoblastoma" is suggested for this group of ossifying bone sarcoma, which should be considered a distinct subdivision of the general group of sarcoma arising in bone. Further study may reveal that all osteogenic sarcoma is malignant osteoblastoma.

FROM THE AUTHORS' CONCLUSIONS.

PROGNOSIS IN MAMMARY CARCINOMA IN RELATION TO GRADING AND TREATMENT. E. K. DAWSON and M. C. TOD, Edinburgh M. J. **41**:61, 1934.

The importance for prognosis in mammary cancer of the absence or the presence of invasion of axillary lymph nodes is brought out by a consideration of the percentages of survivals in the literature. This finding draws a dividing line between favorable and unfavorable cases, and apparently outweighs all other data, such as duration and type of growth and age of the patient at operation. The clinical grading of mammary cancers on the basis of extension of growth, checked when possible by histologic examination, seems necessary in all attempts to estimate prognosis and evaluate treatment. Various methods of histologic grading described in the literature are discussed, with special reference to such appearances as differentiation and anaplasia, fibrosis and lymphocytic cell infiltration. A combination of anatomic (topographic) and cytologic features is suggested as the basis of histologic grading, with emphasis on the position rather than on the type of the malignant cells. This method combines clinical and histologic findings as interdependent factors influencing prognosis.

FROM THE AUTHORS' SUMMARY.

THE HEALING OF INTRA-DUCT CARCINOMA OF THE MAMMA. R. MUIR and A. C. AITKENHEAD, J. Path. & Bact. **38**:117, 1934.

Two cases of Paget's disease of the nipple are recorded in which the associated intraduct carcinoma had at places undergone retrogression and disappeared. This occurred by reactive change in the intra-elastica connective tissue, which underwent hyperplasia and, as the cancer cells atrophied, produced obliteration of the lumen. The obliterated ducts ultimately were represented by hyaline material, often avascular and relatively acellular, surrounded by a ring of abundant elastic tissue. These changes were observed mainly in the ducts in the deeper part of the nipple and in the subadjacent tissue, but also in the substance of the breast.

FROM THE AUTHORS' SUMMARY.

ARGENTOPHIL FIBRILS IN THE DIFFERENTIAL DIAGNOSIS OF MALIGNANT TUMORS. F. ASCHER, Beitr. z. path. Anat. u. z. allg. Path. **92**:1, 1933.

This is the first of twenty rather short articles that make up a number of the *Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie* issued in honor of the seventieth birthday of K. Buday of Budapest. Ascher examined ninety-seven malignant tumors by various histologic procedures, including silver impregnation methods for the demonstration of reticulum fibrils. Forty-four of the tumors were certainly epithelial in origin, forty were sarcomas, and in thirteen classification was difficult. The tumor cells of none of the epithelial tumors formed intracellular argentophil fibrils. All of the sarcomas formed such fibers. The group difficult of classification included Krukenberg tumors, lympho-epithelioma, mixed tumor of the parotid gland, seminoma of the testis and carcinosarcoma. All of these Ascher considers carcinomas because of the absence of the formation of argentophil fibrils by the essential tumor cells.

O. T. SCHULTZ.

Society Transactions

LOS ANGELES PATHOLOGICAL SOCIETY

C. M. HYLAND, *President*

Regular Meeting, Oct. 9, 1934

ADENOMA OF THE PARATHYROID GLAND. ROY W. HAMMACK.

A white woman, aged 50, had had a swelling in the neck, without symptoms of hyperthyroidism for ten years. She has had joint pains for nine years, and the joints were becoming stiff, so that walking was interfered with. On March 23, 1934, she fell and injured the right humerus. She appeared well nourished. A firm egg-shaped mass in the region of the thyroid gland, to the right of the midline, pushed the trachea markedly to the left, without obstructing the respiratory tract. Roentgenographically a supracondylar fracture was shown, which was treated by open reduction. At operation marked thinning of the bone cortex was noted. Subsequent x-ray photographs showed extensive and pronounced thinning of all the long bones. No bone cysts were shown. In repeated tests from April 7 to May 7, the blood serum showed from 11.8 to 13.9 mg. of calcium per hundred cubic centimeters, and 1.9 and 1.8 mg. of phosphorus, and on April 28 the blood phosphatase was 0.3 unit.

At operation, May 9, a tumor was removed from the posterior and inferior aspects of the right lobe of the thyroid gland. Immediately after operation the serum calcium was 14.7 mg. and five and a half hours later 13.3 mg. The next day, May 10, the calcium was 9.1 mg., and May 11, 8.1 mg.; the serum phosphorus was 2 mg. On repeated tests from May 14 to August 9, the calcium gradually rose from 8.4 to 9.8 mg., and the phosphorus from 1.8 to 3.6 mg. After operation no tetany developed, but calcium lactate was given by mouth, and parathyroid extract was injected. The patient's symptoms disappeared and she was generally improved following operation, feeling better than for years. On August 9, study of x-ray photographs of the osseous system showed no increase of calcium content.

The tumor was oval and encapsulated, measured 6.5 by 4.5 by 3.3 cm., and weighed 45 Gm. On one side was a thin patch of thyroid tissue. Externally the tumor appeared brown with some red and yellow mottling. The cut surface was light brown with some mottling and homogeneous except for a few small smooth-walled cysts, the largest 1 cm. in diameter, and a few thin fibrous trabeculae. The cysts contained clear fluid with numerous cholesterol crystals. Microscopically the tumor presented small solid alveoli or strands of large pale cells, with rather small round nuclei, distinct nuclear membranes and diffuse chromatin. The blood vessels were numerous and very thin-walled. The cysts were lined by large pale cuboid cells. No fat was demonstrated by sudan III. It appeared to be a true adenoma of the thyroid gland without evidence of malignancy.

The facts supporting the conclusion that this was a parathyroid tumor are (1) the hypercalcemia and low blood phosphorus, characteristic of hyperparathyroidism, with the levels returning to normal after removal of the tumor; (2) the skeletal changes, and (3) the location and the structure of the tumor.

ADENOLYMPHOMA (ORBITAL INCLUSION ADENOMA) OF THE PAROTID GLAND. ERNEST M. HALL.

A white man of 48 entered the hospital on June 4, 1934, on account of a hard, smooth, well circumscribed, tender swelling in the region of the left parotid gland. This had developed "suddenly" about one year before. Roentgenologic examination following injection of iodized poppy-seed oil 40 per cent into the ducts revealed

a normal duct system, indicating that the tumor did not grossly involve and distort the parotid gland. At the time of admission the swelling was acutely inflamed. Following subsidence of the inflammation the tumor was surgically removed.

The tumor was oval and covered by a thick fibrous capsule; it measured 5 by 4 by 3.5 cm. The cut surface showed many cystic spaces, the largest 0.5 cm. in diameter, filled with yellowish-gray granular material surrounded by grayish-white fibrous strands. Near the center there was a broken-down area which measured 1.5 cm. in diameter. Smears of the cyst contents revealed no bacteria, and cultures produced no growth.

Microscopically the loose connective tissue capsule contained small hemorrhages and round cell infiltrations about the blood vessels. Immediately below the capsule was a thick layer of lymphoid tissue containing areas of fibrosis. The central portion of the tumor was composed of cysts lined by a double row of epithelial cells. The cells bordering the lumen were very tall and columnar, with the nuclei near the surface. The epithelium was not ciliated. Smaller conical-shaped basal cells lay between the taller ones. The epithelium rested on a thick stroma of lymphoid reticular tissue with many lymph follicles. In a few places knoblike papillary processes projected into the cysts. These were composed of lymphoid tissue covered with epithelium. With Mallory's aniline blue-orange G-fuchsin stain, streams of dark red hyaline secretion could be seen between the tall epithelial cells, emptying into the cystic spaces. Within the latter was a mixture of red hyaline and blue granular secretion. In places the intercellular red streams were continuous with blue-colored streams within the cysts. The hematoxylin and eosin preparations showed a moderate number of polymorphonuclear leukocytes and cholesterol crystals scattered through the granular contents of the cysts.

Jaffé (*Am. J. Cancer* **16**:1415, 1932) stated that only twenty-one tumors of this type have been reported. The tumors are benign, none having recurred following excision. The chief interest lies in the origin and development of these tumors. They are believed to be derived from some vestigial structure in the region of the parotid gland. The views of Albrecht and Artz (*Frankfurt. Ztschr. f. Path.* **4**:47, 1910), Hamperl (*Virchows Arch. f. path. Anat.* **282**:724, 1931) and Kraissl and Stout (*Arch. Surg.* **26**:485, 1933) on the histogenesis of the adenolymphoma were discussed.

CARCINOMA OF THE STOMACH WITH SKELETAL AND MENINGEAL METASTASES ASSOCIATED WITH THROMBOCYTOPENIC PURPURA. HUGH A. EDMONDSON.

A white woman of 59 entered the hospital with a history of pain behind the left ear gradually increasing for one month and paralysis of the left side of the face for three days. Later, evidence of marked disturbance of the ninth and tenth cranial nerves also developed. Because of tenderness over the mastoid, a mastoidectomy was done, but no gross pathologic changes could be found. Later general purpura appeared, associated with a platelet count of 82,000, a bleeding time of fifteen minutes and a clotting time of ten minutes, with incomplete clot retraction. Before death she began to vomit blood, and a large left supraclavicular node was noted.

At necropsy a carcinoma of the stomach was found which had spread beneath the mucosa of the cardiac portion of the stomach and lower third of the esophagus. There were extensive metastases to the perigastric, peribronchial, left supraclavicular and periaortic lymph nodes, pancreas, liver, kidney, adrenal glands, thoracic vertebrae, petrous and mastoid portions of the left temporal bone and the left portion of the sphenoid. The dura over most of the left cerebral hemisphere and especially in the posterior and middle fossae was covered with a vascular brownish layer of tumor tissue which also had small extensions in the leptomeninges. The left lateral sinus and internal jugular vein through the jugular foramen were filled with a tumor thrombus.

Microscopically the tumor was a carcinoma simplex, but in certain regions there was some mucus formation as well as glandular arrangement. Everywhere

the tumor showed a tendency to invade veins. Many tumor emboli were seen in the alveolar capillaries of the lung. Metastatic carcinoma completely filled the left lateral sinus and some of the smaller cerebral veins, and small masses of tumor cells were seen in many places in the subarachnoid space. On the inner surface of the dura the tumor cells were in small groups in a thick framework of fibrous stroma and in gigantic dilated newly formed capillaries. Metastases in the temporal bone showed tumor cells in the marrow spaces with bone destruction and absence of bone formation.

The mechanism of the thrombopenic purpura in gastric carcinoma is not well understood (Lawrence and Mahoney: *Am. J. Path.* **10**:383, 1934). That in this patient it probably was not due to simple destruction of red marrow is suggested by the disproportionate decrease of platelets in comparison with the other types of cells in the blood. Unfortunately the marrow of the long bones was not examined, but all the lumbar vertebrae were sectioned and, in contrast to the thoracic vertebrae, presented no gross evidence of extensive metastases.

Meningeal metastases from carcinoma of the stomach are comparatively rare (Eusterman and Wilbur: *M. Clin. North America* **15**:7, 1931). Other interesting features are the symptoms calling for exploration of the mastoid and the carcinomatous occlusion of the lateral sinus.

GELATINOUS CARCINOMA OF SIGMOID FLEXURE IN FIFTEEN YEAR OLD GIRL. HOWARD A. BALL.

A girl of 15 was admitted to the hospital after progressive abdominal enlargement for two months, amenorrhea for six months, recent nausea and lumbar pain. She was normal in stature but undernourished and anemic. The abdomen was symmetrically enlarged, with tense skin, dulness in the flanks and a fluid wave. The provisional diagnosis was tuberculous peritonitis. She had considerable lumbar pain, and there was much vomiting. The temperature was rarely above normal and then only by half a degree. Moderate leukocytosis was present. The peritoneal fluid had a specific gravity of 1.015, and contained albumin (3 per cent) and 2,200 cells per cubic millimeter, mostly lymphocytes. No acid-fast organisms were demonstrated, and the fluid was culturally sterile.

At laparotomy, iliac and mesenteric lymph nodes were found enlarged and matted together, and the peritoneum was studded with pinhead-sized nodules. A biopsy revealed no typical tubercles, acid-fast organisms or tumor tissue, but the lymphocytic infiltration was considered consistent with the early stage of tuberculosis. Death occurred ten days later.

At autopsy the thoracic viscera appeared normal. The diaphragmatic pleura and peritoneum were studded with small whitish nodules, while larger plaques and similar nodules covered the entire peritoneal surface. The sigmoid colon for a distance of 15 cm. was inflexible because of greatly thickened walls (1.5 cm.). The lumen was narrowed to a diameter of 1 cm. Adjacent structures were adherent and infiltrated. On section, the tissues presented a gelatinous, semitranslucent appearance. The lymph nodes in the region of the celiac axis were enlarged and matted together. All retroperitoneal nodes were enlarged and, when sectioned, were similar in appearance to the tumor of the sigmoid flexure.

Microscopically the sigmoid flexure showed masses of large ovoid and signet type tumor cells invading the submucosa and distending the mucosal folds. Both the circular and the longitudinal muscle layers were split in numerous places by tumor cells penetrating to the peritoneum. The tumor cells were separated from each other by quantities of gelatinous material, and toward the peritoneal surface there was a rich admixture of lymphoid tissue. The peritoneal tumor tissue and that of the lymph nodes appeared relatively acellular, the great increase in size resulting from the presence of large quantities of gelatinous substance. No mitoses were detected.

The noteworthy features of the case are the unusual age of the patient, the extensive metastases in the serous membranes, the mucinous character of the tumor tissue and the simulation of tuberculous peritonitis clinically and in the biopsy specimen.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 10, 1935

MORTON MCCUTCHEON, *President, in the Chair*

MORPHOLOGIC AND FUNCTIONAL CHANGES ASSOCIATED WITH REESTABLISHMENT OF BILE FLOW IN CATS WITH EXPERIMENTAL OBSTRUCTION OF THE COMMON DUCT. HAROLD L. STEWART and ABRAHAM CANTAROW.

Simultaneous studies were made of the concentration of bilirubin in the serum, the bromsulphalein retention and the morphologic changes in the livers of twenty-nine cats with uncomplicated total biliary stasis produced by ligation of the common bile duct. Data were obtained for almost every twenty-four hour period up to the sixteenth day of stasis. In nineteen animals the ligature was subsequently successfully released, and in seventeen of these simultaneous functional and morphologic studies were performed at different times during periods of decompression of from one to four days' duration; morphologic studies were obtained on the seventh day of decompression.

During stasis, the bile ducts undergo progressive dilatation, mural thickening and mucosal proliferation; the small ducts become markedly proliferated and later undergo regression. Parenchymal regressive changes consist of focal midzonal necrosis, subcapsular and nondescript hyaline necrosis and sporadic nondescript necrosis. The necrotic cells in most situations are constantly replaced by regenerating hepatic cells until the terminal stages of stasis, when the process of regeneration fails. In the subcapsular zone, however, the degenerative changes tend to remain stationary unless complete necrosis supervenes. Organization of the periportal areas of hyaline necrosis eventuates in an extreme degree of concentric avascular fibrosis, with pinching off of the vascular and biliary channels of the involved portal radicles. Evidences of regeneration are present within eight hours, consisting of binucleation, multinucleation and mitosis. Regeneration lags after the fifteenth day.

There was marked individual variation in the concentration of bilirubin in the serum. The highest incidence of maximum bilirubinemia in the group as a whole occurred early in the second week of stasis, the incidence declining during the remainder of the experimental period (sixteen days). There was no consistent relationship in degree between the morphologic changes and the bilirubinemia at any time during the period of total biliary stasis. Individual variation in degree was more marked in bromsulphalein retention than in bilirubinemia and was not consistently related to the duration of stasis or to the concentration of bilirubin in the serum. There was no apparent relationship in degree between dye retention and the morphologic changes in the liver and bile ducts, either in individual instances or in the group as a whole.

Changes in bilirubinemia during stasis may be dependent in part on diminished regeneration of hemoglobin, diminished metabolism of pigment and suppression of bile acid synthesis. The observed variations in dye retention may be dependent on variations in several factors, including destruction, storage and extrahepatic elimination of the dye.

During decompression, diminution in the intensity and extent of pigmentation was extremely variable. In some cases a decrease in the pigmentation of Kupffer cells occurred simultaneously with an increase in that of hepatic cells, suggesting a rapid movement of bile pigment in this direction. Increase in the extent of regressive changes and a rather characteristic disruption of the intralobular architectural pattern, with loosening of the cells from their reticular attachments, were prominent features of the liver during decompression. A rather constant finding was a peculiar vacuolation of the epithelial cells lining the smaller and medium-sized bile ducts and of the associated infiltrating cells. The smaller proliferated

bile ducts tended to regress to the point of disappearance. This occurred simultaneously with, and was perhaps largely dependent on, active regeneration of adjacent hepatic cells, which eventuated in lobular expansion and more or less complete restoration of the parenchyma in these situations. These regenerative changes, in which active mitosis played a prominent part, also occurred sporadically throughout the remainder of the lobule. In the restoration of the hepatic parenchyma, active regeneration was supplemented by recovery of degenerated but still viable cells.

In the great majority of cases the bilirubin in the serum fell promptly following relief from obstruction, and in contrast to the findings during total stasis the dye retention during decompression generally paralleled the bilirubinemia. No consistent relationship in degree could be established between the striking morphologic features of the liver during decompression and the associated changes in bilirubinemia or dye retention: Similar functional observations were made on animals with widely differing morphologic changes in the liver, and widely various functional findings were obtained in animals with practically identical histologic changes.

On the basis of these observations it appears that alterations in the degree of bilirubinemia and of bromsulphalein retention during total biliary stasis and biliary decompression in the cat are dependent, in part at least, on factors other than morphologic changes in the liver and bile ducts.

VACCINATION AGAINST EXPERIMENTAL PNEUMOCOCCIC INFECTIONS. JOHN A. KOLMER and ANNA M. RULE.

1. Rabbits have been actively immunized against type I pneumococcic pneumonia and septicemia produced by intratracheal injections of virulent cultures by oral administration of seven doses of vaccines at daily intervals. Of the three acid-killed, bile-dissolved and milk-heated vaccines employed, the first appeared to produce the most immunity, which has persisted at least four months or longer. Oral administration of similar vaccines prepared from pneumococci of types II and III also produced active immunity but probably not of a degree equal to that engendered by pneumococci of type I.

2. Rabbits have been effectually immunized against meningitis and septicemia following intratympanal and intracisternal injections of virulent pneumococci of types I, II and III by oral administration of vaccines once a day for a week. Particularly encouraging results were observed with hydrochloric acid-killed, sodium taurocholate-dissolved and heat-killed vaccines.

3. In general, the immunization of monkeys (Macacus rhesus) with subcutaneous injections of mixed chemically killed pneumococcus vaccines proved superior to that with oral administration of an acid-killed vaccine of the same strength and dosage. Vaccination against pneumococci of type I was more effective than against those of type II with both vaccines.

4. Intradermal inoculation of adult rabbits with pneumococci of type I after the method of Goodner produced severe local inflammatory reactions characterized by extensive edema along with septicemia, fever and leukocytic changes, terminating fatally in all instances. Less well defined lesions were produced by types II and III, and their severity appeared to bear a relationship to the virulence of the pneumococci for mice.

5. Rabbits have been successfully vaccinated against fatal dermal pneumococcic infection by five subcutaneous injections of a heat-killed vaccine of type I pneumococci. Less effective results were observed on oral immunization. Similar results were observed with subcutaneous and oral administration of vaccines prepared from pneumococci of types II and III.

LOCALIZATION AND DEVELOPMENT OF THE LESION IN EXPERIMENTAL PNEUMONIA. THOMAS FRANCIS JR.

Monkeys of the species Macacus cynomolgus were infected with pneumococci of type III by either the intratracheal or the intrabronchial route. With the former,

the infecting organisms were allowed to drain into the lower part of the trachea through a small catheter, and the animal was tilted toward the side on which the infection was to be localized. With the intrabronchial route, a radiopaque catheter was inserted with the aid of fluoroscopy into the desired secondary bronchus of a pulmonary lobe, and the organisms were then injected through the catheter. With either procedure a disease was produced which closely resembled, clinically and pathologically, lobar pneumonia in man.

By study of daily x-ray photographs of the sick animals, certain data were obtained bearing on the site of localization and the mode of spread of the pneumonic process. When the organisms were introduced intratracheally, the earliest consolidation was found to occur in the portion of the lobe near the hilus and to spread toward the lateral periphery. On the other hand, when the bacteria were implanted in the distal air passages, the earliest lesion was observed in the lateral aspect of the lobe, spreading from there toward the hilus. When extension of the pneumonic process to another lobe occurred, the consolidation was most frequently observed to begin about the larger bronchi and to spread through the respective areas supplied by them.

Microscopic studies were made of fixed sagittal or transverse sections of the entire lung, cut in thicknesses of from 5 to 10 microns the lungs of monkeys which died at various intervals after the onset of the disease being used. By this means it was possible to observe uninterruptedly the different stages of the pneumonic process within a lobe, from the advancing margin to the most complete consolidation, or to study the early stages of the infection in a lobe freshly involved by what might be considered the natural mode of spread.

In general, in the freshly involved lobe, the oldest reaction with deposits of fibrin and few cells is seen about the bronchus or bronchiole. Adjacent to this is an area rich in leukocytic exudate, and this in turn is surrounded by an area in which the alveoli are filled with edema fluid containing numerous pneumococci. At the very edge of the pneumonic process the alveolar spaces may contain edema fluid in which no detectable organisms are present.

Even in the completely involved lobe, similar stages of the process may be observed, and the age of the reaction in a given area appears to depend on the time of involvement of its larger air channel.

Little was noted to suggest that the infectious process spreads by the lymphatic channels or by direct extension through the interstitial tissues. In fact, one may follow the two branches of a bronchiole and find the lumen of one, and the lobule supplied by it, rich in pneumonic exudate, while the other branch and its lobule are practically uninvolved.

The evidence indicates that with type III pneumococcic infections, at least, the pneumonia is bronchiogenic; that the initial consolidation depends on the portion of the bronchial tree in which the infecting material is arrested, and that the infection spreads by dispersion of infected edema fluid directly through the air passages.

NEW YORK PATHOLOGICAL SOCIETY

Anniversary Meeting, Jan. 24, 1935

WILLIAM C. VON GLAHN, *President, in the Chair*

IRVING GRAEF, *Secretary*

CHRONIC GLOMERULONEPHRITIS WITH HYPERPLASIA OF THE PARATHYROID GLANDS AND CYSTIC FIBROUS OSTEITIS. EARL P. LASHER JR. (by invitation).

An 8 year old Italian boy was seen in the service of Dr. S. Z. Levine at the New York Hospital on Aug. 8, 1934, because of his inability to walk, owing to weakness, of twelve months' duration, and anorexia and lassitude of slightly longer

standing. The familial history was not significant, and the child's birth was normal. The development was normal except that the child had suffered from polydipsia, polyuria and enuresis since infancy and had uncomplicated pneumonia at the age of 5 months. The present illness appeared after acute otitis media fifteen months before admission to the hospital and was marked by temper tantrums and capricious appetite, and there were frequent periods when the patient screamed in his sleep. Weakness and pallor became marked, and three months prior to admission to the hospital three copious epistaxes and several "spasms of the hands" were noted.

The patient was thin, poorly developed and lethargic, and presented the mongolian facies and prominent parietal bosses of the skull. The chest was funnel-shaped, and the costochondral junctions were enlarged. The muscles of the lower extremities were atrophied, and a smooth, hard, ovoid enlargement of the proximal end of the right fibula was found. The skin was creamy yellow. Roentgenograms of the skull and long bones showed peculiar granularity of the former and irregularity of the epiphyseal ends of the shafts of the latter with increased concavity in these areas. There were "moth-eaten" foci of decreased density in both tibias and in the right humerus. In addition, there was a multicystic expansion of the upper end of the right fibula with thinning of the cortex about it.

One month later, following slight diarrhea, the patient became drowsy, and five days later he was brought to the hospital in coma. His temperature was 36.8 C.

Results of Chemical Examinations of Blood Specimens

Specimen	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	p_H	Carbon Monoxide, Vols. per Cent	Sodium Chloride, Mg. per 100 Cc.	Serum Protein, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Total Base, Mg. per 100 Cc.
No. 1 (on admission)	3.30	14.80	7.00	6.80	429.00	7.98	118.40	111.30
No. 2 (9 hours later)	3.78	12.50	7.05	18.20	458.00	8.43	.....	106.90
Milliequivalents								
No. 1	....	8.59	....	2.69	73.40	16.76	.....	101.44
No. 2	....	7.25	....	7.29	78.40	18.16	.....	111.10

(101.8 F.). The pulse rate was 120. The systolic blood pressure was 76; the diastolic, 30. The respirations were of the Kussmaul type, with an odor of acetone to the breath. The optic fundi showed nothing unusual, and except for inconstant abnormalities of the deep reflexes the physical examination revealed nothing not already noted. The Trousseau and Chvostek signs were negative. Sixteen hours after admission to the hospital the patient suffered a series of convulsions in which the hands and feet assumed the positions characteristic of tetany. He died during the attack.

A Mantoux test (0.01 mg.) was negative, and a Kline test was negative. The urine was scanty and contained small amounts of albumin and an occasional erythrocyte. There was severe anemia with slight leukocytosis. Two samples of blood were taken for chemical examination, one soon after admission, and the other about nine hours after this.

Autopsy.—The right kidney weighed 50 Gm.; the left, 80 Gm. They were contracted and firm, with adherent capsules, beneath which the parenchymal surfaces were irregularly granular. The cut surfaces showed an increased amount of gray fibrous tissue and a cortex that averaged only 3 mm. in thickness. Microscopically Bowman's capsules showed typical crescents with glomerular adhesions; there were diffuse interstitial fibrosis, cystic dilatation of many tubules and focal lymphocytic infiltration, but no calcium deposits. The left lower parathyroid gland measured 9 by 4 by 5 mm. and weighed 65.6 mg.; the right lower one measured 7 by 12 by 4 mm. and weighed 111 mg., and the right upper one measured 11 by 6 by 3 mm. and weighed 90 mg. None contained nodules. The left upper parathyroid gland was not found. Histologically the glands were similar, and the cells

were all of the "water-clear" type and lay in closely packed columns. The proximal end of the right fibula was expanded into an ovoid mass measuring 6.5 cm. in length and 3 cm. in width; the periosteum and cortex here were intact. On cut section the cortex was thin, and the cancellous portions were poorly calcified and surrounded by red, cystic areas scattered in a matrix of reddish-gray fibrous tissue. The epiphyseal cartilages of the ribs and right tibia, fibula and femur were clear and bordered on a rather wide, irregular, reddened line of poorly calcified cancellous bone. Microscopically the multicystic area in the metaphysis of the right fibula showed imperfectly oriented bony spicules, often encompassed by giant cells. The epiphyseal line of the right fibula showed a narrow zone of provisional calcification, and there was a slight increase in the width of the zone of hypertrophic cartilage. The trabeculae of the primary spongiosa were horizontal and closely packed, and there was no excess of osteoid tissue.

It seems probable that this was a case primarily of chronic glomerulonephritis in which general bone changes occurred due to diminished intake and increased excretion of calcium, and secondarily of hyperplasia of the parathyroid glands which caused a lesion typical of cystic fibrous osteitis in the metaphysis of the right fibula.

DISCUSSION

ROBERT A. MOORE: My associates and I have been interested in this case. I think it presents, as has been brought out by Dr. Lasher, several problems as to the relationship between parathyroid disease and renal disease. It is entirely possible that in this case there are two diseases which are independent of each other. But it is also possible, on theoretical grounds, to unite the two through an acidosis with nephritis which resulted in a loss of calcium. The changes in the bone are certainly not those of rickets. They are not those of the low calcium, high phosphorus rickets which have been described. We should appreciate any opinion which the other members of the society may have regarding the nature of the case.

ECTOPIC CHORIO-EPITHELIOMA. I. E. GERBER.

Two cases of chorio-epithelioma are described. One occurred in a woman, aged 31, from whom no history of a previous pregnancy was obtained. The tumor was in the left lung; the remaining organs were uninvolved. No evidence of a primary tumor was found in the uterus or in its adnexae. The Aschheim-Zondek test was positive. The possible origin of the tumor was discussed.

The second case was that of a retroperitoneal chorio-epithelioma in a man, aged 28. There were metastases to the lungs, liver, kidneys and spleen. The genitalia were entirely uninvolved. No teratomatous elements were found in the tumor. The Aschheim-Zondek test was positive. In view of Staemmler's report of the occurrence of testicular rests in the retroperitoneal tissues, chorio-epitheliomas in males can be accounted for as having their origin in such rests.

DISCUSSION

IRVING GRAEF: It may be of interest to cite another case similar to Dr. Gerber's first one, studied at Bellevue Hospital last fall. A woman of 32 years who entered the hospital in the Third (New York University) Medical Division because of failure of the right side of the heart gave a history of having had a pregnancy followed by an abortion three or four years before admission. She died within twenty-four hours after hospitalization, and few clinical data could be obtained, except that she had intense cyanosis and enlargement of the liver and that roentgenograms showed scanty signs of disease in the pulmonary fields. At necropsy all the medium-sized pulmonary arteries were blocked with soft, necrotic thrombi which had the appearance of a tumor, but no focus could be found for such a metastatic tumor. The uterus was very slightly enlarged (less than one-fifth larger than the average normal size). When the endometrial canal was opened and the uterus sectioned in several planes, no tumor was found. After fixation of the uterus for

several days, many more sections of the organ were made, and one small uterine venous sinus was found which contained a similar tumor thrombus, measuring 0.5 cm. in diameter, attached to the wall of the vein. Microscopically this and the thrombi in the medium-sized pulmonary vessels had the same appearance as shown by Dr. Gerber.

INFECTION WITH TRYPANOSOMA EQUIPERDUM. DAVID PERLA.

This article will be published in full in a later issue of the ARCHIVES.

CERTAIN PATHOLOGIC ASPECTS OF SCHISTOSOMIASIS MANSONI. DOMINIC A. DE SANTO.

Three cases of schistosomiasis Mansoni in which autopsies were made are reported, and a fourth case is mentioned which was subjected to special study by a colleague.

This disease is caused by a trematode worm which infests the human host, entering as a penetrating larval form, or cercaria, and maturing in the portal vein. The lesions are the direct result of oviposition in the various organs which the adult females reach from their habitat in the portal vein.

One case occurred in an inhabitant of Guadeloupe in the West Indies; three cases occurred in young Puerto Ricans, the oldest of whom was 26. Three of the four cases showed characteristic nodular pigmented cirrhosis; the pigment may be an excretion of the adult worm. In the fourth case there were "tubercles" in the liver, but no signs of cirrhosis. In all of the cases splenomegaly was present, the weight varying from 300 to 1,200 Gm. The largest spleen resembled, both grossly and microscopically, that of a patient with Banti's disease.

In one case numerous ova were shown, arranged as "tubercles" in the omentum, and the diagnosis was made by biopsy. In the second case ova and "tubercles" were found in the liver and prostate. In the third case ova were widely disseminated in the liver, kidneys, lungs, myocardium and pancreas.

In two cases, death resulted from ruptured esophageal varices; in the third, death was accidental, and in the fourth it occurred as described by Dr. Clark in the following paper.

In none of the cases were gross intestinal lesions apparent, although one case showed eosinophilic infiltration of the mucosa and subserosa.

If careful examinations of the stools of young Puerto Ricans are made, ova will be found more frequently than is at present supposed. Any pigmented cirrhosis found in Puerto Ricans or West Indians at autopsy is likely to have been caused by Schistosomum Mansoni.

CHRONIC PULMONARY ARTERITIS IN SCHISTOSOMIASIS MANSONI ASSOCIATED WITH HYPERTROPHY OF THE RIGHT CARDIAC VENTRICLE. EUGENE CLARK (by invitation).

A woman with schistosomiasis Mansoni exhibited extensive pulmonary vascular disease associated with hypertrophy and dilatation of the right ventricle of the heart. She was a 21 year old Puerto Rican, admitted to the wards of the Third (New York University) Medical Division of Bellevue Hospital twenty-four hours before her death. She was born in Puerto Rico and lived there until the age of 9; thereafter she resided in New York. Since the age of 14 she had experienced palpitation and shortness of breath on exertion. One month previous to her admission to the hospital dyspnea, orthopnea and swelling of the legs and abdomen were noted. Physical examination revealed the signs of congestive heart failure with ascites.

Necropsy revealed coarse nodularity of the liver, enlargement of the spleen, hypertrophy and dilatation of the right ventricle of the heart, and dilatation and atheroma of the pulmonary artery. The diagnosis of schistosomiasis Mansoni was established by the demonstration of lateral-spined ova of S. Mansoni in granulomatous lesions in fixed sections of the lungs, myocardium, liver, pancreas and kidneys.

The striking observation in the lungs was the granulomatous lesions in the interstitial tissue related to the bronchi and blood vessels. These lesions were characterized by the presence of one or more ova surrounded by young fibrillar tissue in which were spindle-shaped and oval fibroblasts, lymphocytes, eosinophilic polymorphonuclear leukocytes and numerous endothelial-lined channels. Though some represented extravascular granulomas, it was demonstrated from a study of serial sections that the majority were in small pulmonary arteries (from 150 to 200 microns in diameter) the lumens of which had been obliterated by the schistosomal granulomas and the media of which showed severe atrophy and destruction of elastica accompanied by aneurysmal dilatation. Many arteries from 50 to 500 microns in diameter proximal to a granulomatous lesion showed marked diminution of the lumen as a result of intimal thickening and medial hypertrophy. The arteries distal to the granulomatous lesion were normal.

It is believed that the obliterating granulomatous arterial lesions represented a specific productive arteritis due to the presence of the ova of S. Mansoni. The intimal thickening and medial hypertrophy of the vessels proximal to the lesions represented a nonspecific arteriosclerotic change attributable to the obstruction ahead. The atheroma and the dilatation of the pulmonary artery and the hypertrophy and dilatation of the right ventricle were similarly a response to the impedance in the small pulmonary arteries.

DISCUSSION

DAVID PERLA: My interest in schistosomiasis is rather indirect. I have had a number of sections sent me from a co-worker in Puerto Rico and from Japan. A long, interesting monograph on schistosomiasis was written by a Japanese about ten years ago; he reviewed about seventy-five cases, among which he mentioned one of very unusual type that I should like to describe to you. He found an instance of schistosomiasis associated with enormous splenomegaly, and he said that such an association was not infrequent. The splenomegaly is due not so much to the secondary cirrhosis of the liver as to a thrombosis of the splenic vein resulting from an invasion of the blood stream by large numbers of worms from the liver which proceed into the splenic veins, causing occlusion of these veins and in that way enlargement of the spleen.

From Puerto Rico I received material showing lesions of an unusual type of schistosomiasis. The lesions were characterized by an acute miliary tubercle-like dissemination. This is a rare type in which one finds miliary tubercles quite like those of tuberculosis or syphilis spread throughout the body, unassociated with the parasites. Of course, one finds the parasites in the liver, but the widespread miliary tubercle-like dissemination is not associated with them.

I should like to ask Dr. De Santo if that peculiar picture in the spleen, with fibrosis and pigment, is not like the so-called nodular siderosis with iron pigmentation and a peculiar yellowish discoloration of the tissue.

In regard to splenectomy in the treatment of schistosomiasis, a more careful perusal of the literature would have prevented its use. I think it is contraindicated. Its use for schistosomiasis is dangerous, and it is usually followed promptly by death. I was informed by a colleague in China that the use of splenectomy for kala-azar is almost always followed by death, and that its use in the treatment of chronic malaria has been abandoned for the same reason. There is an immediate flare-up of the disease with death of the patient.

I should like to know how Dr. De Santo knows that the parasite lives for forty years. I do not doubt that, but I should like to know how the conclusion is arrived at that a group of parasites live in the body for fifteen, twenty or forty years. Second, I should like to know whether these parasites are alive, or whether this is a reaction to an encysted parasite which is no longer viable? Has any one tried to transplant such organisms into other parts of the body or into other animals to see whether they can be transmitted in that way? I should also like to know whether anything is known about how the ova get where they are. It is hard to imagine large organisms wandering around. Do they arrive as ova,

or do they arrive in some other way and assume this peculiar appearance? Are you sure that what you see are ova? Finally, what is known about the mechanism of resistance to parasites of this type? Are antibodies demonstrable? Is there any type of skin reaction? I know that Taliaferro has prepared antigens from worms and has succeeded in getting antigenic fractions, and that he has found patients whose skin is sensitive to these fractions.

DOMINIC A. DE SANTO: I can understand Dr. Perla's question about how one knows that they are ova, because some of the photographs are not clear. However, it is always possible to find some ova about which there can be no doubt: They have the characteristic lateral spine and the highly refractile chitinous membrane.

As to the longevity of the worms, there has been some work done on that, particularly with Bilharzia, and some also with S. Mansoni. For example, in the first case that I mentioned the man had been out of the tropics for eight years and was still passing live ova, which shows that these worms must have been alive for almost eight years. Cases have been reported in which soldiers who acquired bilharzial schistosomiasis during the Boer War were passing live ova in the stools after twenty or thirty years, and those ova were known to be alive because they could be hatched out as miracidia in fresh water. So I do not think there is any question about the longevity of the worms. The longevity of the worms of Bilharzia, however, is probably greater than that of the worms of S. Mansoni.

As to the mechanism of the distribution of the eggs, they are deposited in the sites where they are found. The female migrates during the season of ovulation and invades the various organs against the blood current from the portal system, so that the ova are found predominantly in the liver, pancreas and intestine and, by way of the anastomotic circulation, in the bladder, prostate and other organs. The distribution to organs that are away from the portal system is difficult to understand, and I have not encountered any satisfactory explanation. It seems likely that some eggs are swept into the right chambers of the heart and from there spread into the pulmonary capillaries (which is a bit difficult to understand), or it may be that they penetrate the pulmonary veins and then have a peripheral distribution, for they have been found, as in Dr. Clark's case, in the peripheral organs and even in the brain, and I do not know how that can be explained unless one assumes a hematogenous distribution.

With the immunologic responses in this disease I am but vaguely familiar. There is a skin test that has been developed, in which an antigen is used which is made from the livers of infested snails, and the technic of that test is something like the technic of the Frei test. There is also a complement-fixation test in which a similar antigen is employed. Just how reliable these tests are, I do not know.

With reference to the other question, as to the changes in the spleen, I do not think those changes are specific, because, as I pointed out, they are practically identical with those seen in many cases of so-called Banti's disease. They consist of the deposition of iron, calcium and silicon in the trabeculae and diffuse fibrosis of the pulp. Possibly in many of its characteristics the lesion may be associated with old thrombosis of the splenic vein.

Book Reviews

Report of the Medical Research Council for the Year 1933-1934. Presented by the Lord President of the Council to Parliament by command of His Majesty, January 1935. Price, 3 shillings. Pp. 172. London: His Majesty's Stationery Office, 1935.

In the introduction are reviewed the major activities of the Medical Research Council under the following headings: clinical research, research into mental disorders, inheritance and disease, the natural history of epidemics, tuberculosis among African natives, influenza, chemical problems of bacteriology, chemical control of the nervous system, sex hormones, accident proneness and road dangers and the measurement of vitamins. Then come sections on the National Institute for Medical Research, the determination of biologic standards and the methods of biologic assay and measurement, the department of clinical research in University College Hospital, external research schemes, industrial health and traveling fellowships. An interesting review is given of the work at the National Institute for Medical Research on viruses, the effects of bacterial toxins on the brain, bacterial chemistry and immunology, protistology, the chemical transmission of nervous effects, pharmacologic chemistry, carbohydrate metabolism, sterols and related substances, chemotherapy, prolonged inhalation of tar dust and sex hormones. The section on external research schemes reviews the work in many institutions on a variety of medical problems which is aided by grants from the council. There are good indexes of scientific subjects, institutions and names of persons. Encouraging progress is recorded in the promotion of clinical research as a career by the establishment of new posts "for whole-time work, offering reasonable prospects of advancement and security such as already exist in the laboratory branches of medical science." The report presents a vivid and instructive account of the activities of the Medical Research Council, which derives its main support from the government. There can be no question about the rapid advancement of research under the influence of the council. The report will be of interest not only to those who are concerned with the promotion of research in general but also to investigators and students who wish to follow closely investigation in various medical fields.

CORRECTIONS

Two errors occurred in abstracts of articles from the *Deutsche Ztschr. f. d. ges. gerichtl. Med.*, appearing in the February issue of the ARCHIVES (**19**:267, 1935), i. e.:

In the abstract of the article by I. Moharren, entitled, "Demonstration of Group-Specific Substances in Organs Fixed with Solution of Formaldehyde," "takes," at the end of the first line, should read "lakes."

In the following abstract, of the article by C. Hallauer, entitled, "Blood Grouping on Small Quantities of Blood Stain," the word "agglutinins," in the third line, should read "agglutinogens."

In the proceedings of the December 27 meeting of the New York Pathological Society, in the April issue (ARCH. PATH. **19**:599, 1935), a stenographer's error occurred in the last sentence of the second paragraph on page 601, in Dr. Alfred Plaut's discussion of his paper, entitled, "Metastasizing Tumor of the Pineal Body." This sentence should read, "It was possible to demonstrate," etc., instead of, "It was not possible to demonstrate," etc.

Books Received

On the Occurrence of Lymphogranulomatosis (Sternberg) in Sweden 1915-1931 and Some Considerations as to Its Relation to Tuberculosis. Martin Uddströmer. Acta Tuberculosea Scandinavica, supplementum I. Pp. 225. Copenhagen, Denmark: Levin & Munksgaard, 1934.

The Technique of Post Mortem Examination as Practiced in the Pathological Institute of McGill University at the Royal Victoria Hospital, Montreal. Compiled by D. R. Coman, M.D., C.M., Assistant to the Institute and Demonstrator in Pathological Anatomy. Pp. 47, with 12 illustrations. Montreal: Renouf Publishing Company, 1935.

This booklet describes clearly the method of postmortem examination at the Royal Victoria Hospital in Montreal. The description is limited to examinations for clinicopathologic purposes only, and no directions are given for the procedure for medicolegal purposes. There are a suitable number of blank leaves for notes. Twelve simple black and white figures illustrate the description. There are no directions as to how to describe the appearances of the tissues and organs. There is nothing new or original in the method, which is essentially that introduced years ago by Virchow in his "Sections-Technik." The booklet will be helpful to any one who is beginning to learn how to perform autopsies in other than medicolegal cases.

Experimental Bacteriology, in Its Applications to the Diagnosis, Epidemiology and Immunology of Infectious Diseases. Dr. W. Kolle, Director of the Institute for Experimental Therapy and of the Chemicotherapeutical Research Institute "Georg Speyer-Haus," Hon. Professor at the University of Frankfurt, and Dr. H. Hetsch, Professor at the Institute for Experimental Therapy, Frankfurt. Translated from the seventh, completely revised German edition by Dagney Erikson. The English version, incorporating further revision, edited by John Eyre, F.R.S. (Edin.); F.Z.S.; M.D.; M.S.; D.P.H.; Director of the Bacteriological Department, Guy's Hospital; Professor of Bacteriology, University of London. Price, $16. Pp., volume I, 592; volume II, 613, with 118 plates and 200 text figures. New York: The Macmillan Company, 1935.